



UNIVERSITÀ DEGLI STUDI DI PARMA
DEPARTMENT OF CHEMISTRY, LIFE SCIENCES AND
ENVIRONMENTAL SUSTAINABILITY

PhD in Chemical Sciences
XXXIV CYCLE

Catalytic strategies to trigger challenging Diels-Alder cyclisations under mild conditions

Coordinator: Prof. Alessia Bacchi

Supervisor : Prof. Giovanni Maestri

PhD Student: Nicola Camedda

2019-2022

Introduction	5
Pericyclic reactions	6
The dehydro Diels-Alder reaction	8
Thermal dehydro Diels-Alder reaction	9
The photo didehydro Diels-Alder reaction	13
The Didehydro Diels-Alder reaction	17
 CHAPTER 1	
 Ambient Synthesis of Tricyclic Naphthalenes via Stepwise Styryl-yne Dearomative Diels–Alder Cyclization	22
Introduction	23
Results and discussion	25
Conclusions	32
Experimental section	33
 CHAPTER 2	
 Mild dearomative Diels-Alder cyclizations via sequential catalysis	85
Introduction	86
Results and discussion	88
Conclusions	96
Experimental section	97

CHAPTER 3

Functionalization of Alkenyl C–H Bonds with D₂O via Pd(0)/ Carboxylic Acid

Catalysis	147
Introduction	148
Results and discussion	150
Conclusions	157
Experimental section	158

CHAPTER 4

Inter/Intramolecular Cascade of 1,6-Enynes Catalyzed by All-Metal Aromatic Tripalladium Complexes and Carboxylic Acids

	186
Introduction	187
Results and discussion	190
Conclusions	199
Experimental section	200

REFERENCES	262
-------------------	-----

INTRODUCTION

Pericyclic reactions

Pericyclic reactions are one of the most powerful tools for the construction of a wide range of complex molecules. Most of these reactions proceed in a single concerted step through the *cyclic transition state*.¹ The word *concerted* means that breaking and forming of bonds occur generally without the presence of intermediates. The word *pericyclic* is referred to the movement of electrons around a cycle.

Pericyclic reactions can be classified in four types (Figure 1):

Electrocyclic reaction: Concerted cyclisation of a conjugated π -electron system by converting one π -bond to a ring forming σ -bond. The reverse reaction is called *electrocyclic ring opening*.

Sigmatropic rearrangement: Migration of a σ -bond to a new position along an unsaturated system.

Cycloaddition reaction: Two unsaturated reagents combine together in order to form a cyclic adduct thanks to the formation of new sigma bonds, at least one from each component.

Group transfer reaction: Transfer of one atom or groups from one molecule to another following a concerted manner.

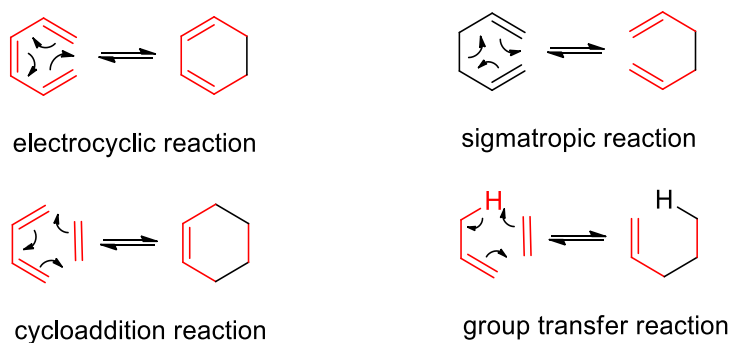
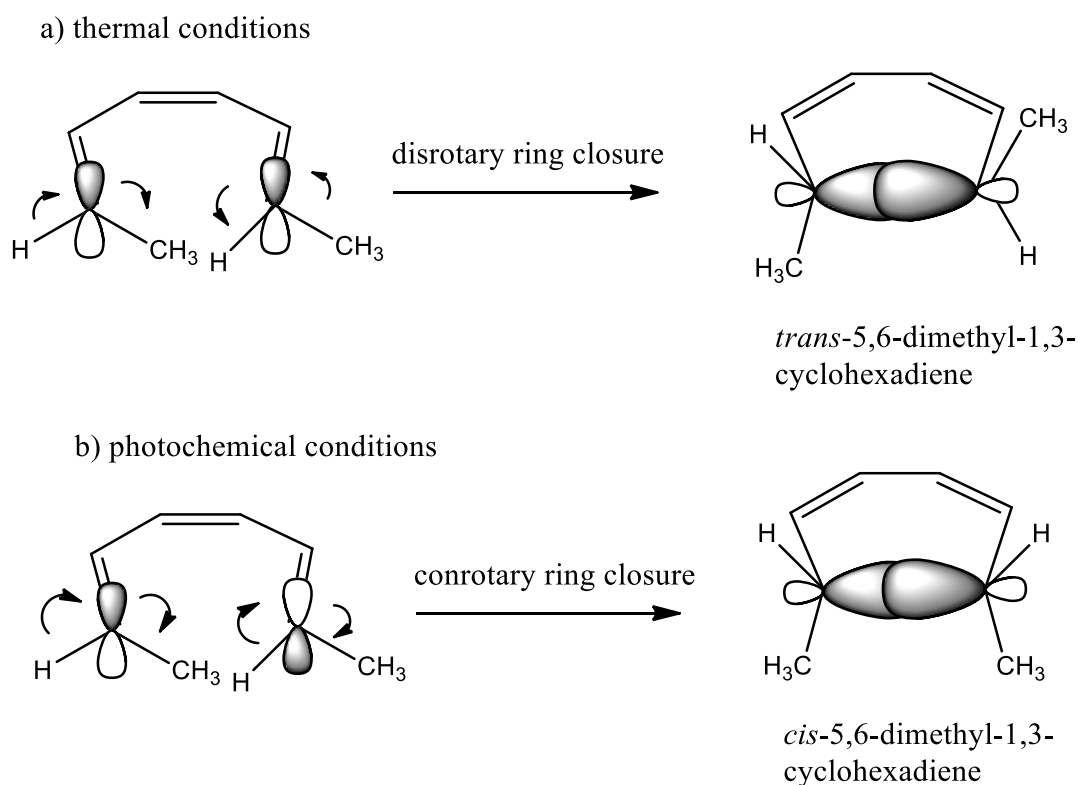


Figure 1. Pericyclic reactions

They can be promoted by heat or irradiation enabling from the same reactant, the obtainment of products with different stereochemistry. The electrocyclic reaction of (2*E*, 4*Z*, 6*Z*)-octa-2,4,6-triene which affords 5,6 dimethyl-1,3-cyclohexadiene can be promoted by heat or irradiation (Scheme 1). In thermal conditions the reactant affords *trans*-5,6-dimethyl-1,3-cyclohexadiene. In this case the HOMO is symmetrical (the two terminal atomic orbitals are identical to each other, Scheme 1, a) and the reaction is allowed for symmetry. The orbital overlap is achieved through a disrotary ring closure. In photochemically conditions we need to consider the HOMO in the excited state. In this case the molecular orbital is antisymmetric. The reactant undergoes a conrotary ring closure affording *cis*-5,6-dimethyl-1,3-cyclohexadiene (Scheme 1, b).



Scheme 1. Stereochemical changes employing light or thermal conditions

Amongst cycloadditions, The Diels Alder reaction is one of the most powerful synthetic routes for the preparation of cyclohexene frameworks. Although its application in industry accounts for only 5-11% of C-C bond forming reactions^{1a}, It is widely used in total synthesis for the construction of complex molecules.² It is a [4 + 2] cycloaddition (Figure 2) between a diene (generally the electron rich reactant) and a dienophile (the electron poor one) and it can exist in a huge range of forms¹. It displays generally a concerted mechanism, albeit there are some cases of stepwise ones.³

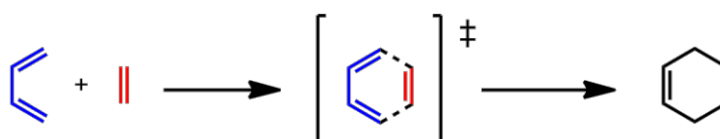


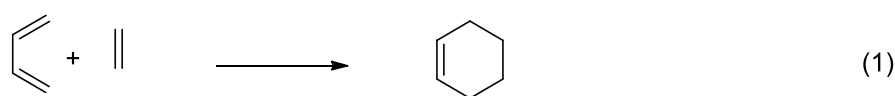
Figure 2. The Diels-Alder reaction

¹ Kumar, S.; Kumar, V.; Singh, S.P. *Pericyclic reactions, A Mechanistic and Problem-Solving Approach*, **2015**.^{1a} Funel, J., Abele, S. *Angew. Chem. Int. Ed.* **2013**, 52, 3822 – 3863. ²Nicolau, C. K.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, 41, 1668-1698. 8112. ³ Wakayama, H.; Sakai, S. *J. Phys. Chem. A* **2007**, 111, 13575.

The Dehydro Diels-Alder reaction

During the last century the understanding of steric and electronic effects occurring in Diels-Alder reactions increased a lot and many variants have been developed. If one double bond from a diene is replaced by a triple one (see Figure 3) the cycloadduct has two commulated double bonds and a high ring strain. Therefore the cyclic allene, in contrast to the classical DA, in order to reduce its significant ring strain, undergoes other transformations and so rearranges. This type of cyclization is so called *Dehydro Diels-Alder reaction*.⁴

Diels-Alder reaction



Dehydro Diels-Alder reaction

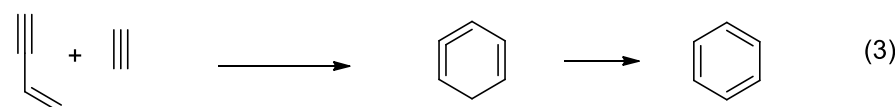
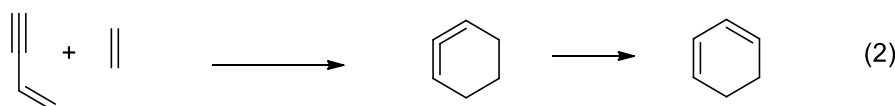


Figure 3. Subdivision of Dehydro Diels Alder reaction according to the degree of saturation

This subdivision was made according to the degree of saturation. Reactions between enynes and alkenes affords isomers of dihydrobenzenes (2) while benzene derivatives are produced by enynes and alkynes (3). Performing DDA reactions generally requires harsh conditions for the reasons highlighted above. Dehydro Diels-Alder reactions can be promoted by heat (*Thermal dehydro Diels-Alder reaction*) or irradiation (*Photo dehydro Diels-Alder reaction*). Further discussions of them will focus only on DDA type 3 in which the double bond of the reactant is part of an aromatic ring.

⁴Wessing, P.; Müller, G.; *Chem. Rev.* **2008**, 108, 2051–2063

The thermal dehydro-Diels-Alder reaction

The first example of thermal DDA was the dimerization of phenylpropionic acid derivatives. In the presence of acetic anhydride they enable the formation of cyclic anhydrides (Figure 4, a). Afterwards other similar approaches were studied employing different starting materials such as ethyl esters (b) and propynoyl chlorides (c).⁵ Generally these reactions were performed at 160-200 °C.

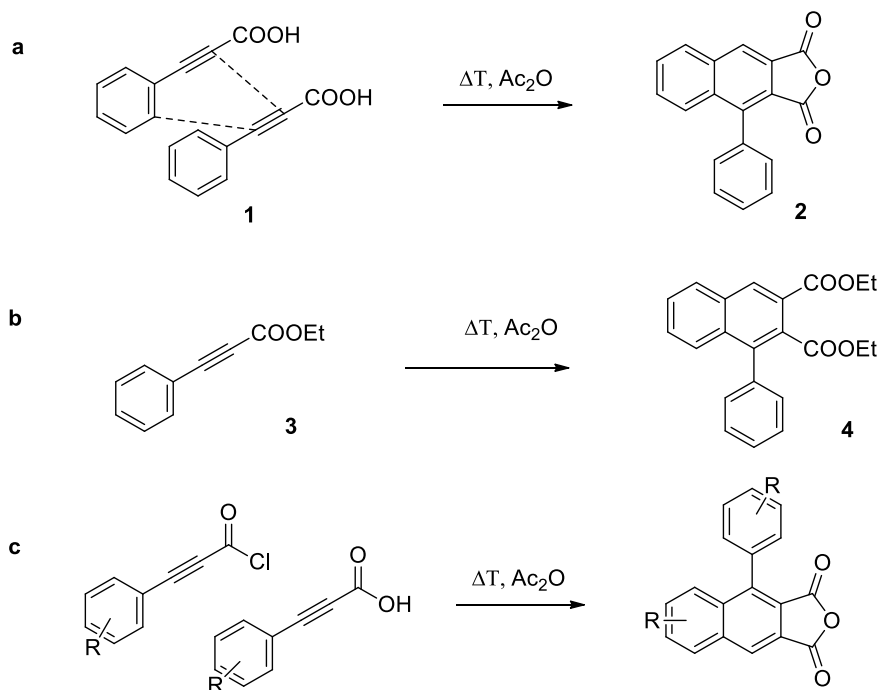


Figure 4. Thermal DDA promoted by propylic acid derivatives

Regiocontrol was generally provided by functional groups into the aromatic rings. If reagents were 3,4 disubstituted two different products may be produced (so called “*o,o'*-selectivity”). In the case of **5**, only **6** and not **7** was formed, maybe for steric reasons (Figure 5) Whereas bromo-substituted acids could afford a mixture of products, iodo-substituted ones provided preferentially naphthalenes **9b** (Figure 6).⁶

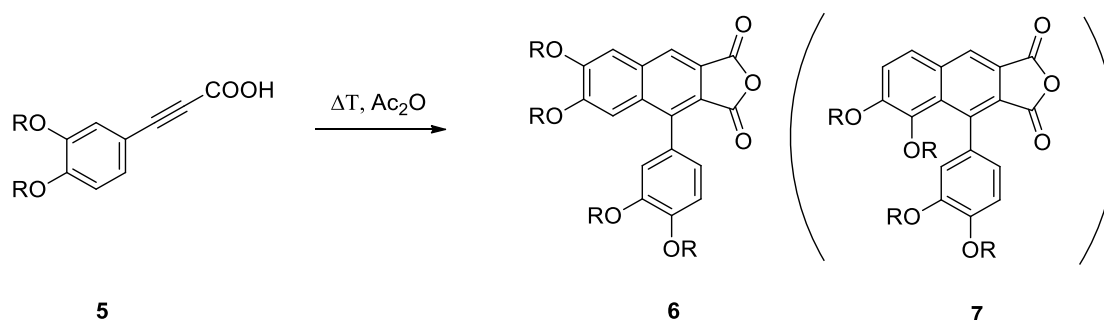


Figure 5. DDA promoted by 3,4 disubstituted reagents

⁵ (a) Michael, A.; Bucher, J. E. *Chem. Ber.* **1895**, 28, 2511. (b) Michael, A.; Bucher, J. E. *Am. Chem. J.* **1898**, 20, 89. (c) Bucher, J. E. *J. Am. Chem. Soc.* **1908**, 30, 1244 (d) Pfeiffer, P.; Moller, W. *Chem. Ber.* **1907**, 40, 384. ⁶ Baddar, F. G.; Moussa, G. E. M.; Omar, M. T. *J. Chem. Soc.* **1968**, 110.

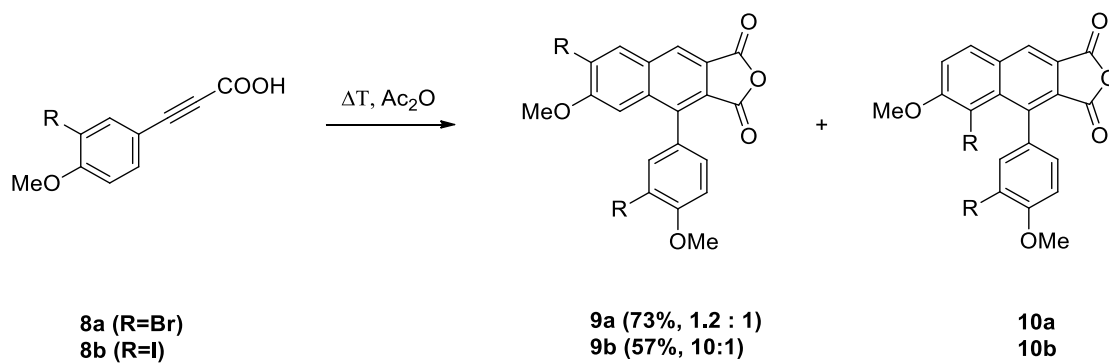


Figure 6. DDA of bromo and iodo substituted propylic acids

Moreover regioselectivity could be achieved if aromatic rings were differently substituted, (so called “*Ar,Ar'*-selectivity”). While reaction between **11** and **12a** produced preferentially the isomer **13a**, this selectivity was not accomplished when a -NO₂ group was introduced (Figure 7).

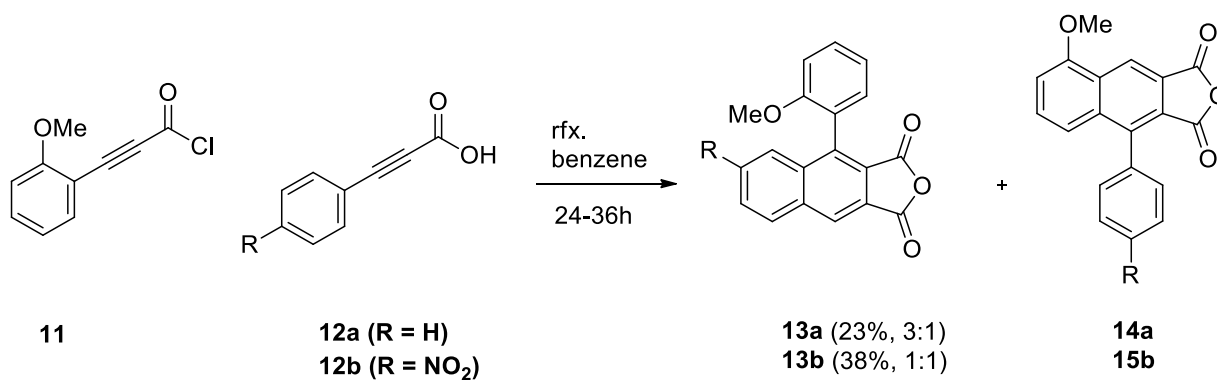


Figure 7. “*Ar,Ar'*-selectivity

From 1950 Klemm and co-workers reported many examples of DDA employing dynes **14** and **17** as starting materials. In the presence of acetic anhydride they afforded a mixture naphthalene or naphthalimide derivatives.(Figure 8).⁷

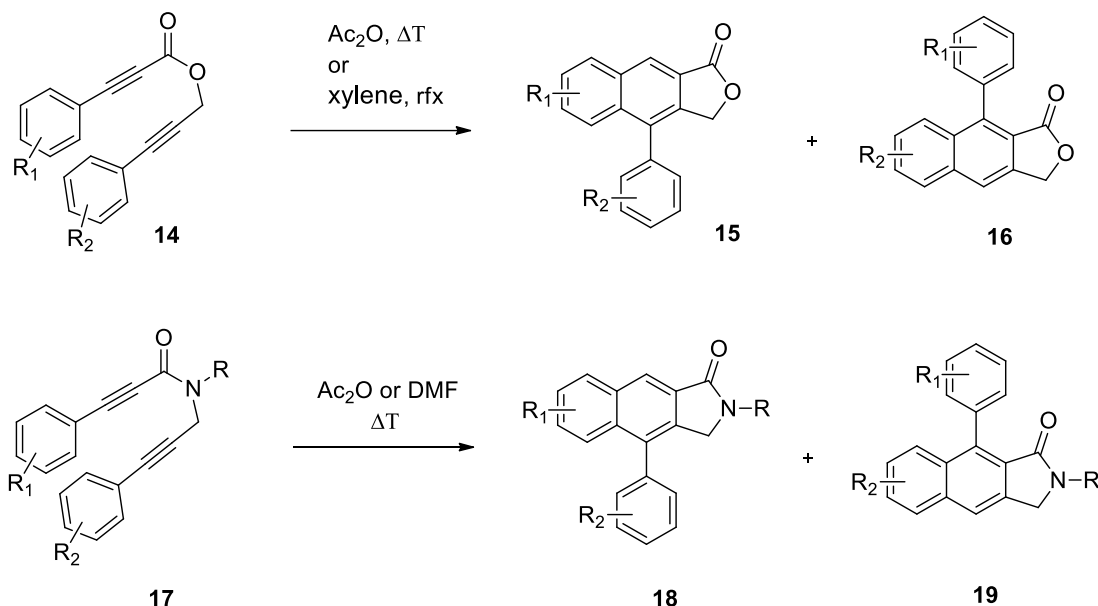


Figure 8. DDA performed with dynes

If the amide **20** has one of its phenyl rings replaced by a TMS, it affords preferentially product **22** in the presence of toluene. Conversely, the same substrate, undergoing DDA reaction, provided **21** if the reaction was performed in Et_3N at $160^\circ C$. (Figure 9).

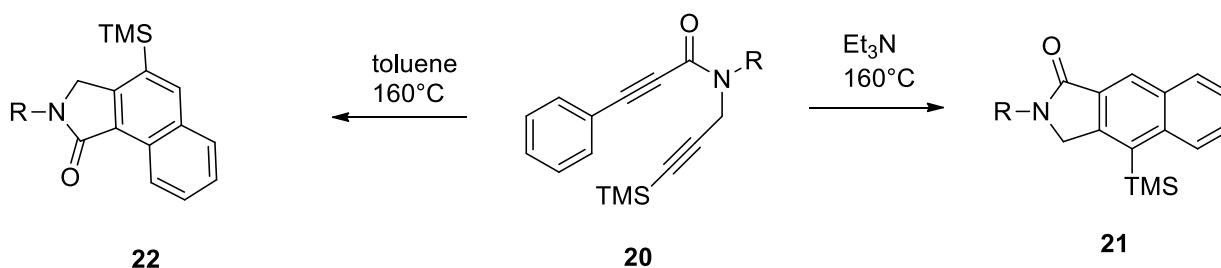


Figure 9. Influence of the solvents in DDA promoted with dyne **20**

⁷(a) Klemm, L. H.; Gopinath, K. W.; Hsu Lee, D.; Kelly, F. W.; Trod, E.; McGuire, T. M. *Tetrahedron* **1966**, 22, 1797. (b) Klemm, L. H.; Hsu Lee, D.; Gopinath, K. W.; Klopfenstein, C. E. *J. Org. Chem.* **1966**, 31, 2376. (c) Klemm, L. H.; Klemm, R. A.; Santhanam, P. S.; White, D. V. *J. Org. Chem.* 1971, 36, 2169. (d) Klemm, L. H.; McGuire, T. M.; Gopinath, K. W. *J. Org. Chem.* **1976**, 41, 2571. (e) Anastas, P. T.; Stevenson, R. *J. Nat. Prod.* **1991**, 54, 1687. (f) Stevenson, R.; Weber, J. *J. Nat. Prod.* **1989**, 52, 367.

These results were also confirmed by deuterium labelling experiments and computational studies which highlighted how the allene **A** evolved into product **21** or **22** (Figure 10).⁸ In the absence of acid or base the blue pathway is favored. According to DFT calculations, conversion of allene **A** to **B** is highly exothermic ($\Delta H^{0K} = -16.7$ kcal/mol) and the resulting allene **D** is 1.4 kcal/mol more stable than **A**. The presence of the base triethylamine accelerates the deprotonation-protonation step from the primarily formed cycloallene (**A** $\rightarrow$ **21**) and suppresses its rearrangement (pathway in blue).

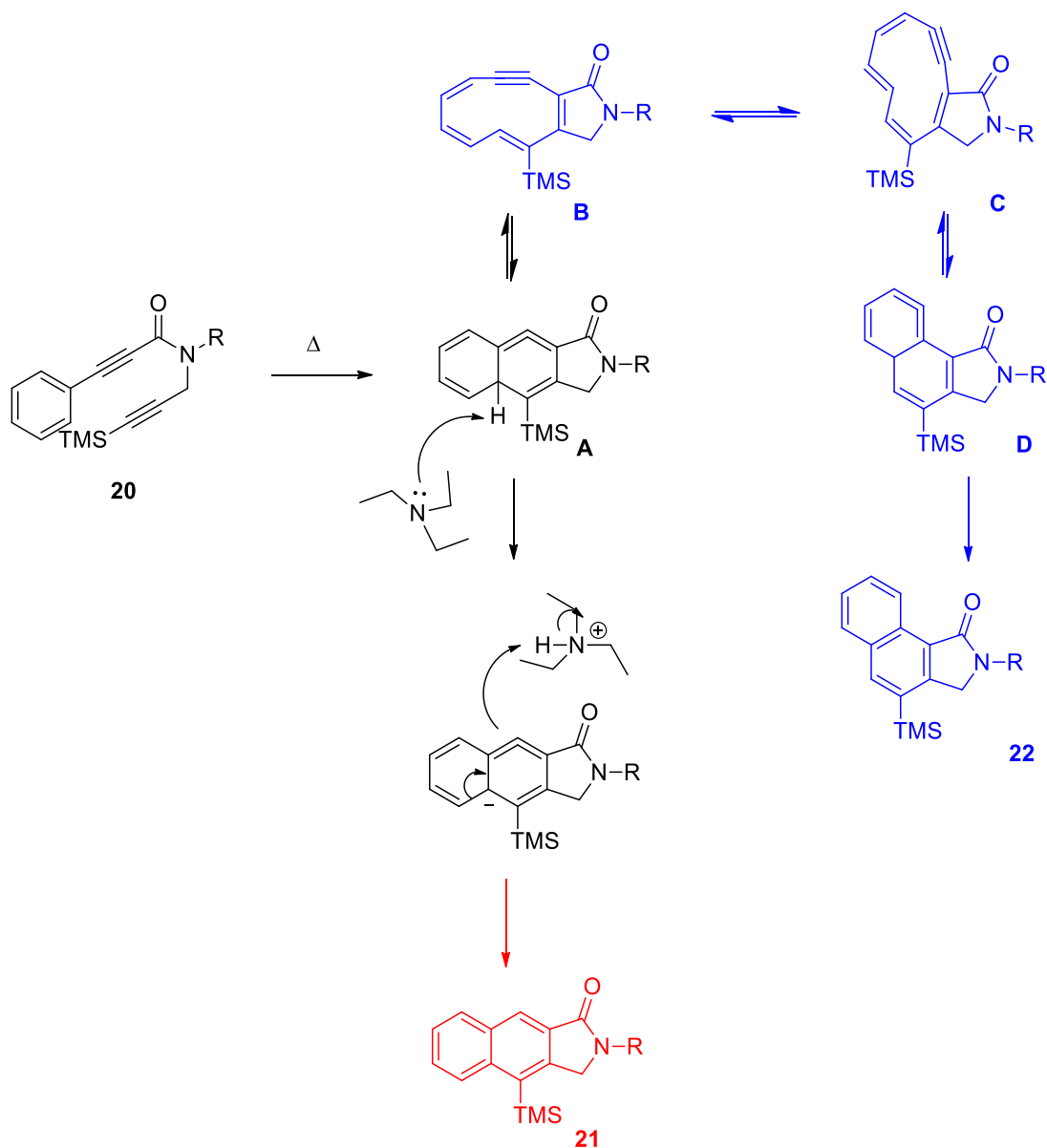


Figure 10. Reaction mechanism of DDA employing reactant **20**

⁸Rodriguez, D.; Vasquez, A., Castedo, L., Dominguez D.; Saa', C. *J. Am. Chem. Soc.* **2001**, 123, 9178-9179

The photo-dehydro-Diels-Alder (PDDA) reaction

The mechanism of a PDDA is highlighted in the figure 11. Photo-excitation of the arylalkyne **23** and following reaction with alkyne **24** allows the formation of the biradical 1,3 butadiene **25**. Ring closure promoted by radical center *b* to the *ortho* position of the benzene ring affords the highly strained cumulene **26**. Then, the cyclic allene rearranges to the aromatic **27** through proton migration ⁹ (Figure 11).

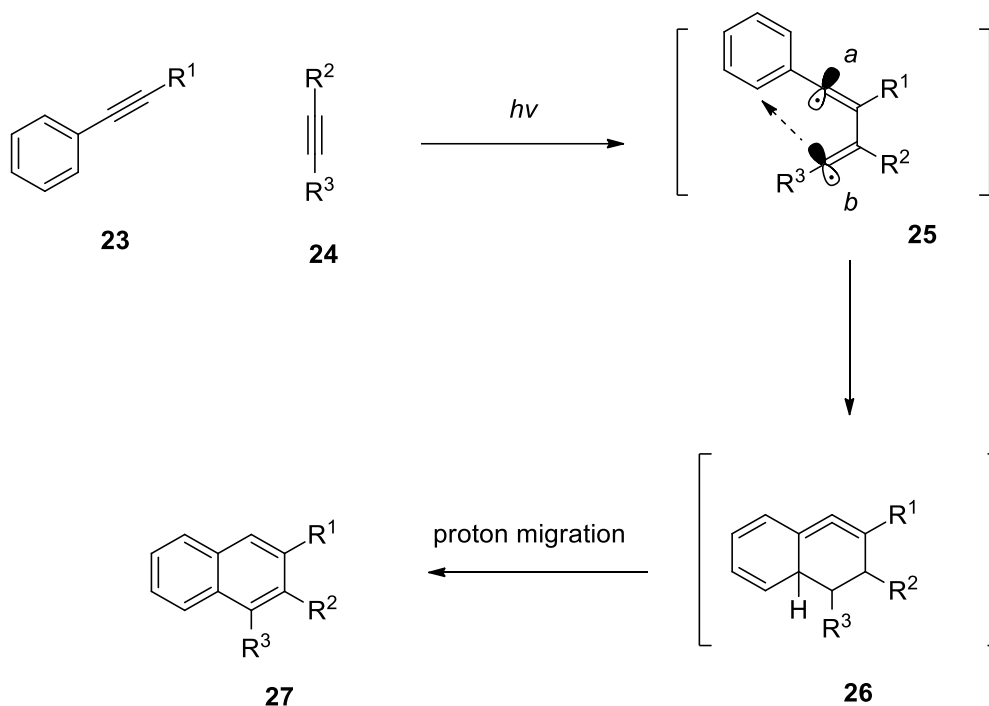
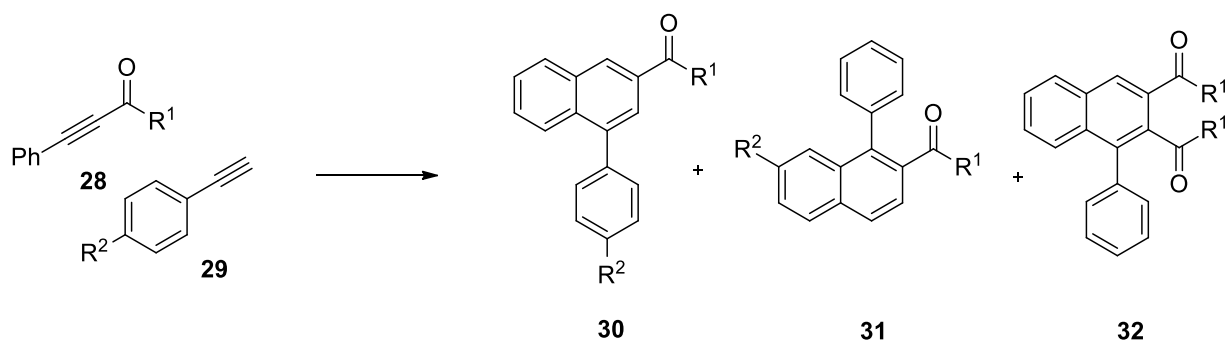


Figure 11. Reaction mechanism of a PDDA

⁹Wessig, P.; Matthes, A.; Pick, C., *Org. Biomol. Chem.*, **2011**, 9, 7599-7605

Ynone **28** in the presence of irradiation and phenylacetylene **29**, provides a mixture of three products. Solvents and functional groups into the aromatic rings have a key role in providing a regioselective reaction. When R^2 is a -H or -MeO (entry 1 and 3, Figure 12) the reaction affords a mixture of products.¹⁰ Conversely, when R^2 is a -SO₂Me (entry 4) and R^1 is a propyl group (entry 2) the reaction affords preferentially product **30**.

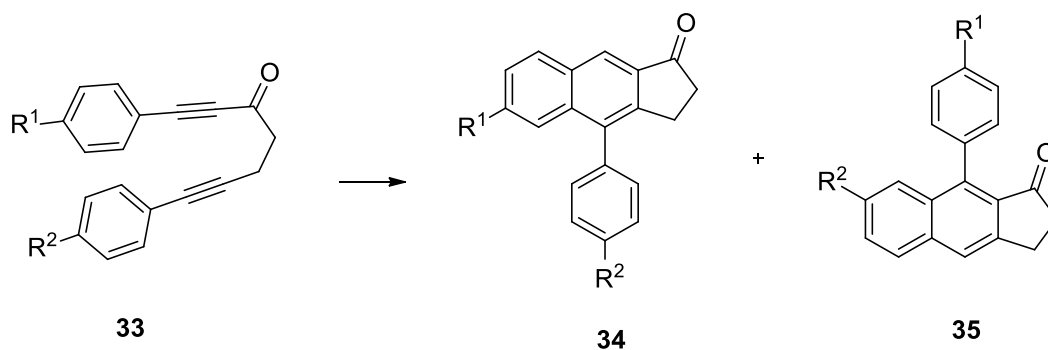


Entry	R ¹	R ²	Solvent	30	31	32
1	Me	H	tBuOH	32%	4%	20%
2	Pr	H	tBuOH	39%	0%	6%
3	Me	OMe	MeOH	21%	12%	0%
4	Me	SO ₂ Me	MeOH	35%	0%	0%

Figure 12. Regiocontrol of the reaction employing ynone **28** and phenylethyne **29**

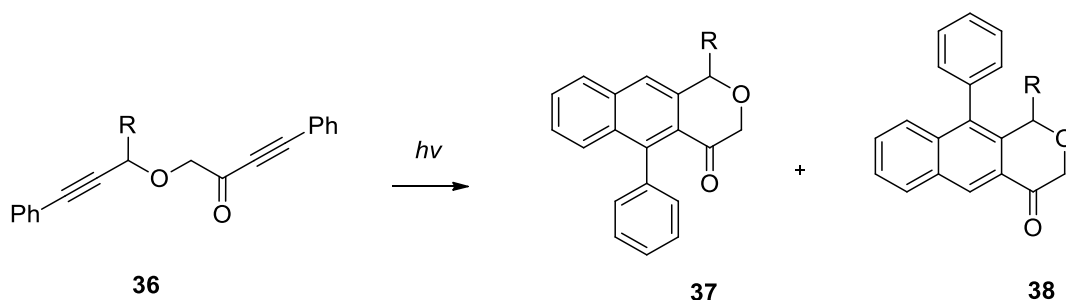
¹⁰P. Wessig, G. Muller, C. Pick and A. Matthes, *Synthesis*, **2007**, 464.

More recently Wessig and co-workers introduced 1,6-diyn-3-ones as reactants. Regiocontrol was achieved through functional groups into the aromatic rings. When R¹ is a -MeO, reactant **33** (Figure 13, entry 1) provides a mixture of products **34** and **35**. Conversely, a -CF₃ (entry 2) allowed the selective formation of **35**.^{10,11} In the case of substrate **36** introduction of bulky groups such as *tert*-butyl led the only isolation of product **37** (entry 5, Figure 14).¹²



entry	R ¹	R ²	34 (%)	35 (%)
1	-OMe	-H	32	55
2	-CF ₃	-H	8	61

Figure 13. Regiocontrol achieved with electron rich and electron withdrawing groups

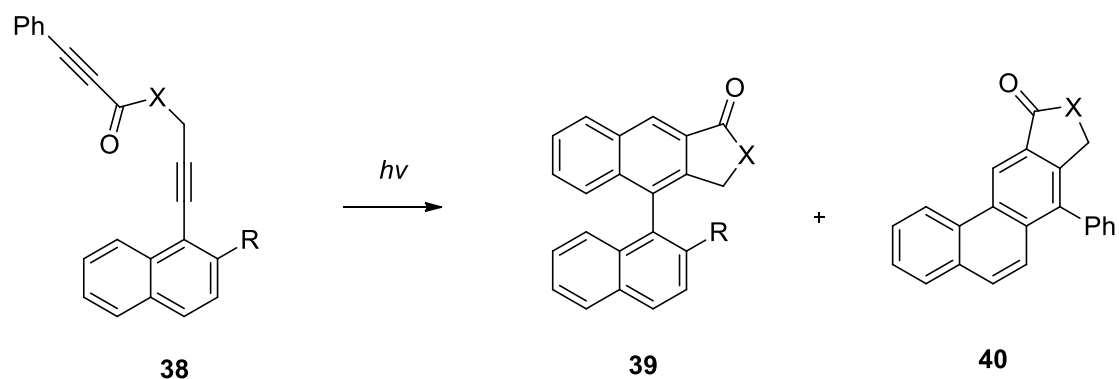


entry	R	37 (%)	38 (%)
1	H	43	34
2	Me	41	27
3	iPr	34	21
4	Ph	43	19
5	tBu	41	-

Figure 14. Regiocontrol with bulky groups

¹¹ P. Wessig, G. Muller, A. Kuhn, R. Herre, H. Blumenthal and S. Troelenberg, *Synthesis*, **2005**, 1445. ¹²P. Wessig, G. Muller, R. Herre and A. Kuhn, *Helv. Chim. Acta*, **2006**, 89, 2694.

Fascinated by this approach, Muller and Wessing in 2006 extended this method to the synthesis of 1,1'-binaphthyls.¹³ These frameworks are widely used in asymmetric catalysis and were obtained by PDDA employing diynes bearing a 1-naphthyl moiety in one of the two alkyne arms. Introduction of functional group -OMe at the 2-position of the naphthyl arm allowed the regioselective formation of the product **39** (entry 2, Figure 15).



entry	R	X	Products
1	-H	O	39 (38%), 40 (41%)
2	-OMe	O	39 (46%)

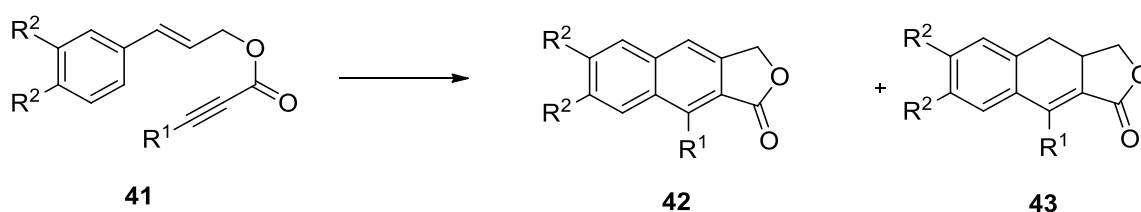
Figure 15. Synthesis of 1,1'- binaphthyls

¹³P. Wessig and G. Muller, *Chem. Commun.*, **2006**, 4524

Didehydro-Diels-Alder reaction of styryl-ynes

Didehydro Diels-Alder reactions caught the attention of many scientists during the last two decades. Its trigger requires the activation of styryl-ynes as starting materials, substrates containing one triple bond and a conjugated diene in which one of the double bonds is a part of an aromatic ring. Generally this cyclisation is performed in very drastic conditions because the energetic barrier connected to the dearomative cyclisation is very high. Therefore many scientists explored this type of reactivity in order to perform similar strategies under milder conditions.

Klemm reported the first example of didehydro Diels-Alder in 1963.¹⁴ The reaction was conducted at reflux employing styrenyl propiolate **41**. In the presence of acetic anhydride, **41a** (Figure 16, entry 1) provided its corresponding dihydronaphthyl lactone **43a** in 48%. Conversely, **41b** (entry 2) afforded only the naphthalene **42b** in low yield.



entry	R ¹	R ²	Conditions	42	43
1	3,4,5-OMe-C ₆ H ₂ (41a)	OCH ₂ O	Ac ₂ O, reflux, 6h	0% (42a)	48% (43a)
2	H (41b)	OCH ₂ O	Ac ₂ O, reflux, 12-72 h	13% (42b)	0% (43b)

Figure 16. Didehydro Diels-Alder reaction employing styryl-yne **41**

More recently in 2002 Chackalamannil performed similar strategies starting from propargyl cinnamates **44** and accessing dihydronaphthofuranone **47** (Figure 17). Labelling experiments revealed that after intramolecular Diels-Alder, formation of the cycloadduct **45** occurred. A subsequent double bond isomerization afforded tetra-ene derivative **46** which finally rearranged to the desired product *via* Suprafacial [1,5] hydride shift.¹⁵

¹⁴Klemm, L. H.; Gopinath, K. W. *Tetrahedron Lett.* **1963**, 4, 1243. ¹⁵Chackalamannil, S., Doller, D., Eagen, K. *Tetrahedron Lett.* **2002**, 43, 5101–5103

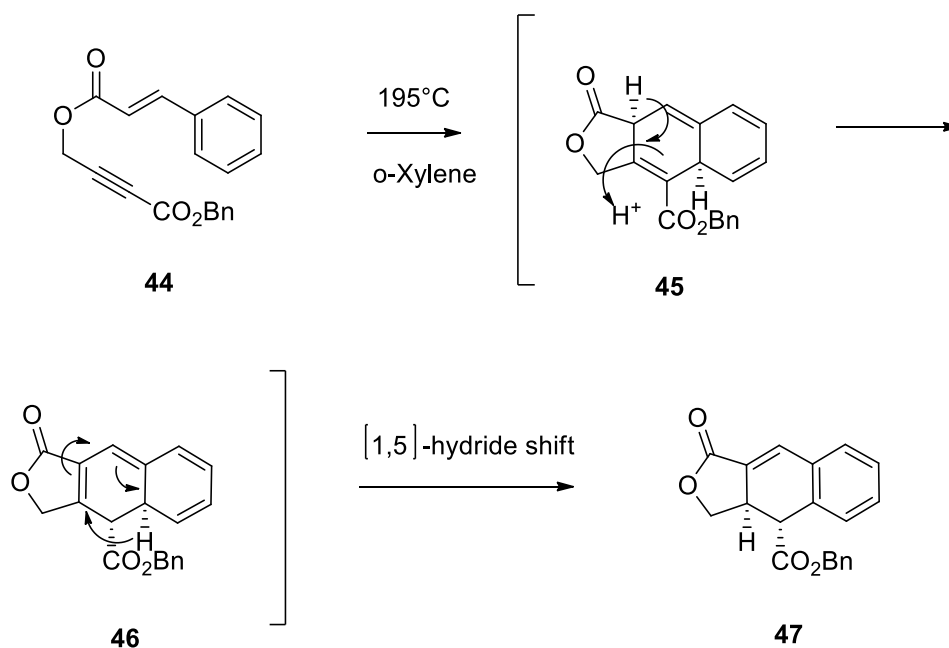


Figure 17. Reaction mechanism of styryl-yne **44**

Similarly, Matsubara in 2011, performing the reaction at 160°C in Xylene, provided tricycle **52** using a styryl-ynes bearing a TMS group attached to the alkyne moiety.¹⁶ It is noteworthy that this approach was regioselective only for naphthalene derivatives. It was proposed that after formation of the cycloadduct **50** a hydrogen elimination occurred maybe due to the higher thermodynamic stability of the resulting polyaromatic cycle **52**. An other chemical explanation could be attributed to the steric repulsive effects of the bulky TMS group, which would accelerate the elimination of hydrogen atoms in spatial proximity (Figure 18).

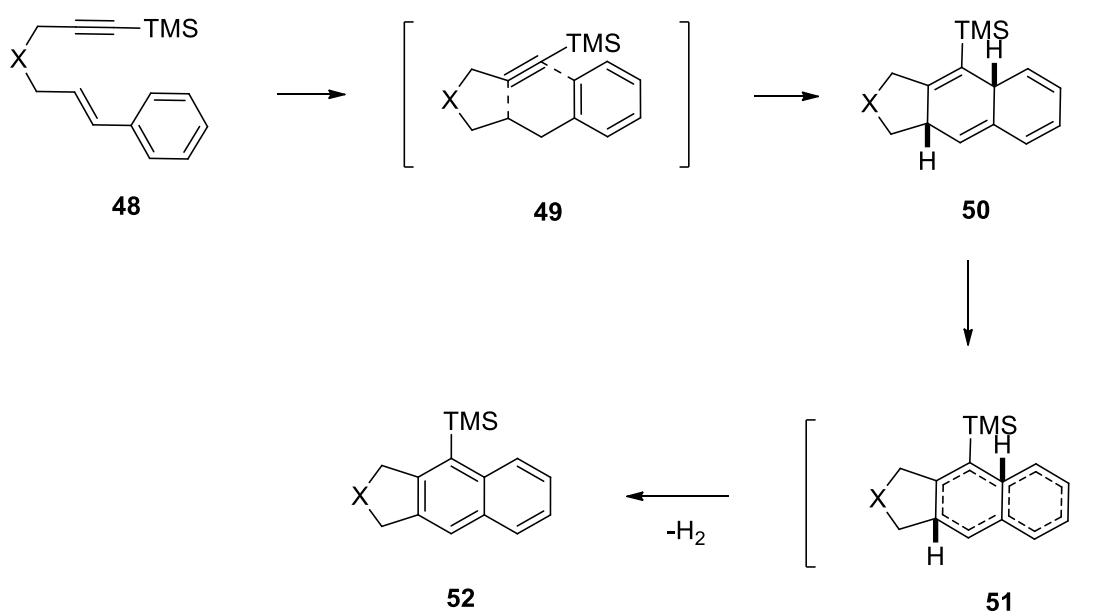
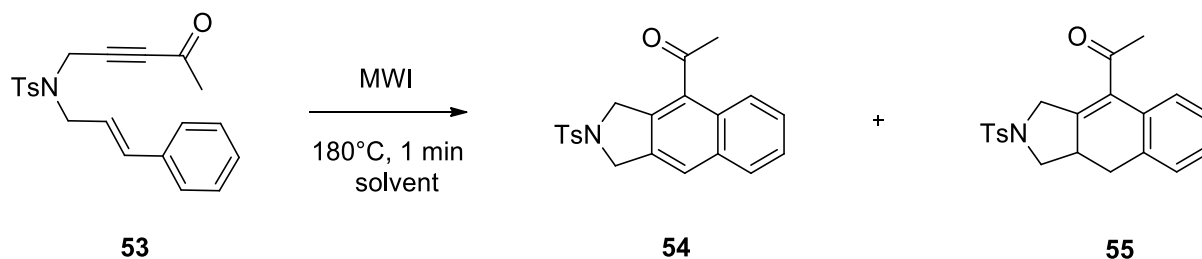


Figure 18. DDA affording naphthalene derivative **52**

¹⁶Ozawa, T., Kurahashi, T., Matsubara, S. *Org. Lett.* **2011**, 13, 5390-5393

Four years later Brummond, studying similar approaches under microwave conditions, afforded a mixture of naphthalene and dihydronaphthalene. She disclosed that solvents played a key role in the regioselective formation of dihydronaphthalene **55** (Figure 19). The reaction affords preferentially dihydronaphthalene derivatives as long as solvent dielectric constant rises.¹⁷ Nitro-benzene, differently from the other solvents, provided only naphthalene **54** probably due to its dehydrogenating properties.



Entry	Solvent	Dielectric constant	54 : 55
1	o-DCM	9.93	1 : 1.2
2	DCE	10.36	1 : 1.8
3	MEK	18.50	1 : 2.6
4	iPrOH	20.18	1 : 4.4
5	PhNO ₂	34.82	1 : 0
6	DMF	36.71	1 : 10

Figure 19. Irradiated mixtures (0.06 M) at 180°C for 1 minute

¹⁷Kocsis, L. S., Kagalwala, H., N., Mutto, S., Godugu, B., Bernhard, S., Tantillo, D., J., Brummond, K., M. J. *Org. Chem.* **2015**, 80, 11686–11698

In 2018 Kang and co-workers, similarly to Brummond, performed DDA reactions under microwave conditions in the presence of two Iron catalysts, Iron (II) acetylacetonate and Iron (III) chloride.¹⁸ Combination of both Iron species allowed the selective isolation of naphthalene derivative **60**. According to labelling experiments and computational studies an Inverse electron demand Diels-Alder reaction occurred, promoted by both iron catalysts (Figure 20). Interaction of Iron (II) catalyst into the styrene moiety decreased the LUMO energy of the diene. Cyclization of **57** affords the tetraene **58**. Then Iron (II) triggered a direct dehydrogenation of the two hydrogens in spatial proximity, providing naphthalene **60**. Meanwhile the Fe (III) species catalyzed the *ene*-reaction affording tricycle **59** which then undergoes dehydrogenation forming **60**.

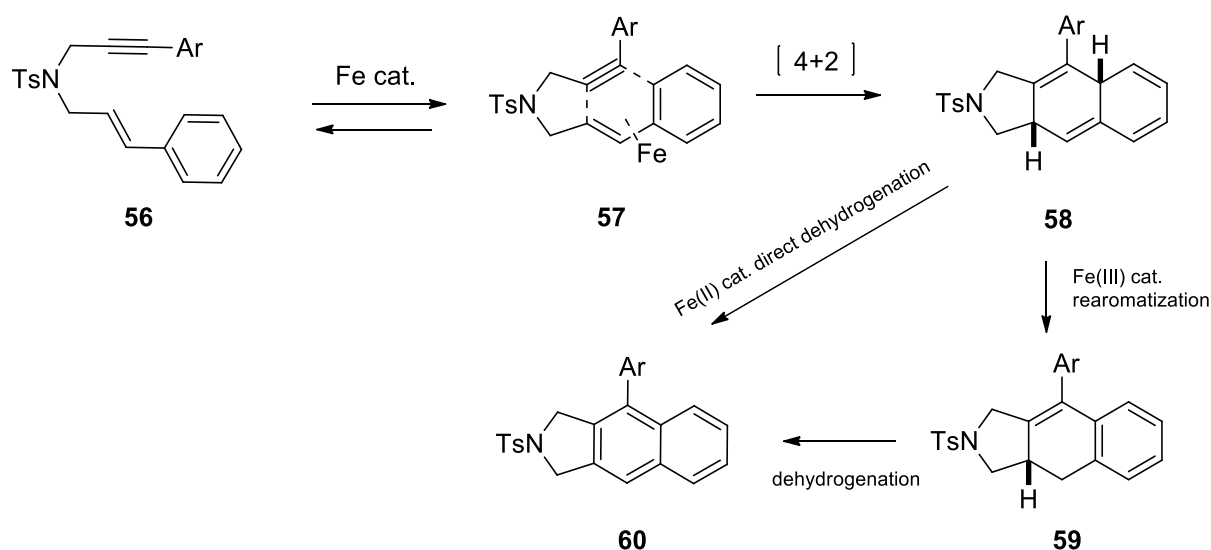
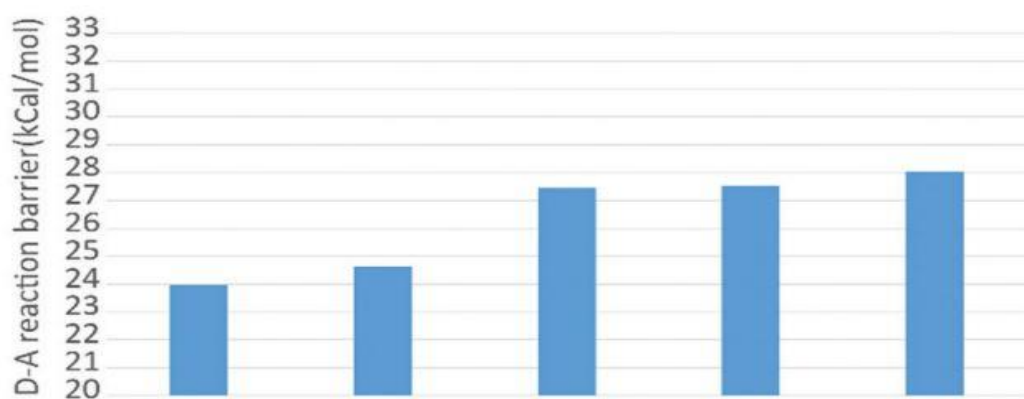
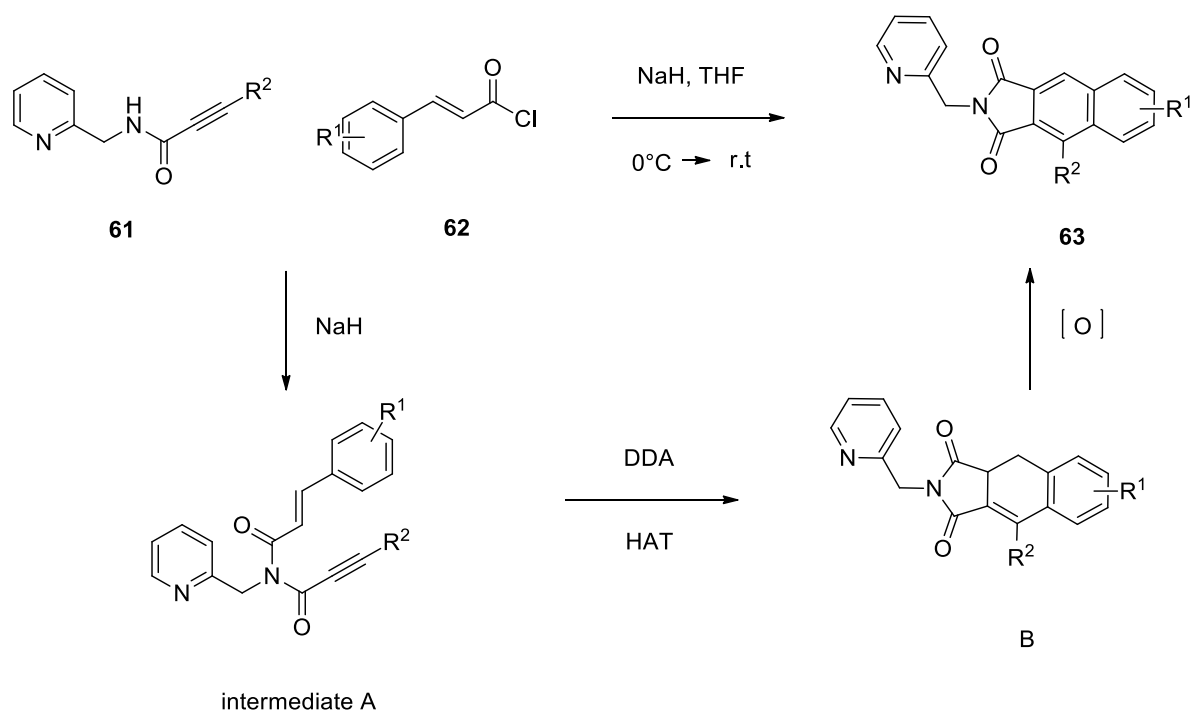


Figure 20. DDA promoted by Iron(II)acetylacetonate and Iron(III)chloride

Surprisingly, Zhang and co-workers reported an Intramolecular dihydro Diels-Alder promoted by sodium hydride employing propiolamides **61** and acyl chloride **62** at ambient temperature.¹⁹ The reaction afforded naphthalimide derivative **63** under very mild conditions without the utilization of transition metals or high temperatures (Scheme 25). Upon an initial S_NAc reaction the intermediate **A** finally converted into the aromatized product **63**. The alkyne part of intermediate **A** acts as dienophile and its styrene arm acts as the diene. Computational studies and experiments revealed the the orbital gap between HOMO and LUMO may be responsible for this reaction. While compounds **B-E** did not afford their corresponding cycles, the imide **A** delivered the desired product probably due to its H-L gap, which is lower compared to the others. (See Figure 21).



	A	B	C	D	E
H-L gap	6.33	6.68	6.77	6.80	7.11
LUMO	-1.46	-0.92	-0.59	-0.59	-1.57
HOMO	-7.78	-7.60	-7.36	-7.40	-7.84

Figure 21. Reaction mechanism and DFT calculations

¹⁸Mun, H. J.; Seong, E. Y.; Ahn, K. H.; Kang, E. J. *J. Org. Chem.* **2018**, 83, 1196 -1203. ¹⁹Chen, X.; Zhong, C.; Lu, Y.; Yao, M.; Guan, Z.; Chen, C.; Zhu, H.; Luo, Z.; Zhang, Y. *Chem. Commun.* **2021**, 57, 5155.

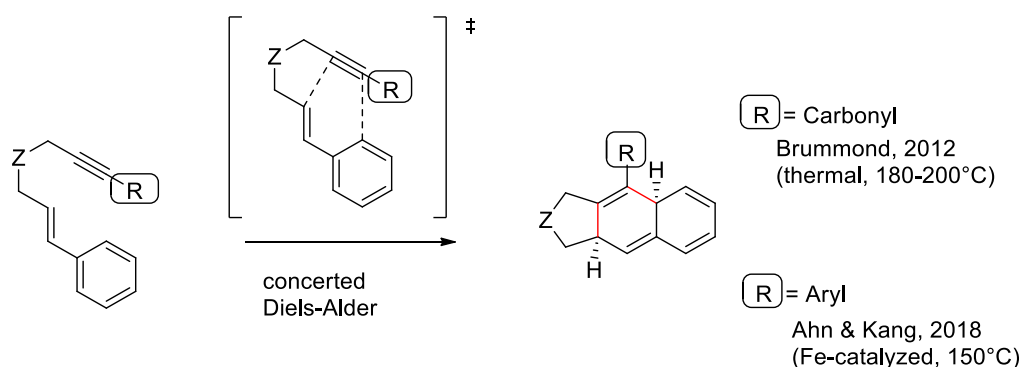
CHAPTER 1

Ambient Synthesis of Tricyclic Naphthalenes via Stepwise Styryl-yne Dearomative Diels–Alder Cyclization

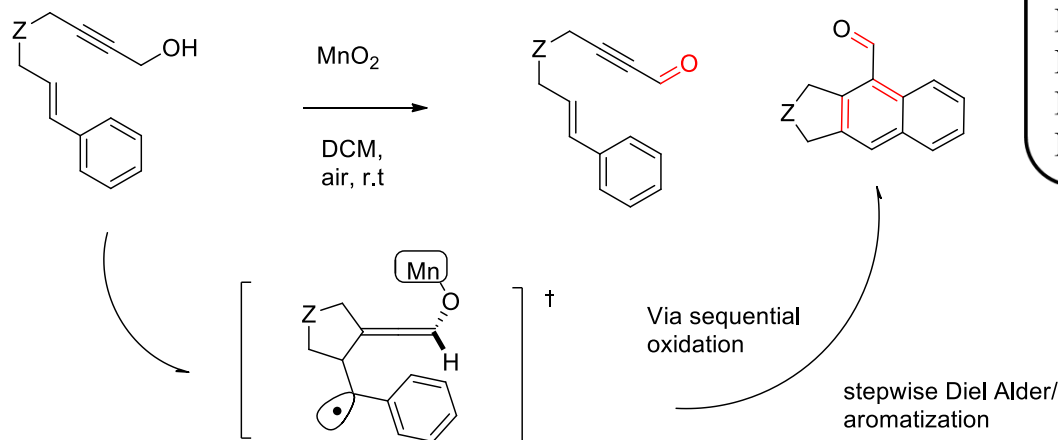
Introduction

As previously reported, The Diels-Alder reaction is one of the most powerful and used reactions in organic chemistry. The Diels-Alder in which vinylarenes are 4- π partners caught the attention of many researchers during the last two decades¹⁵⁻²². However the high temperatures and utilization of transition metals make these synthetic approaches difficult and expensive (Figure 1a). The performance of these intramolecular reactions is marginally improved when the dienophile is a polarized alkyne. In this chapter we report a synthetic method for the preparation of naphthalene derivatives from styrylnols. This reaction is promoted by MnO_2 , which is the cheapest and most abundant source of manganese (Figure 1, b).

a) Challenging dearomative cyclization of styrenynes



b) Present work



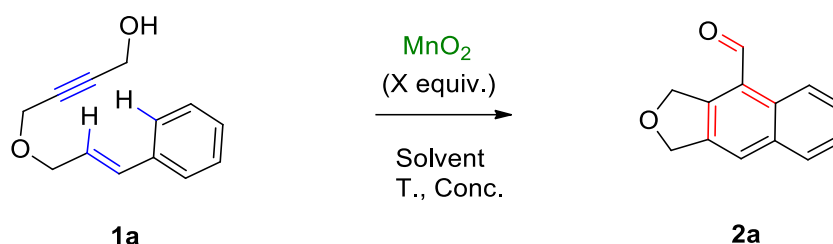
For 100 g	
MnO_2	30.60 €
MnCl_2	>1200 €
$\text{Mn}(\text{OAc})_2$	306 €
$\text{Mn}_2(\text{CO})_{10}$	>2000€
$\text{Mn}(\text{OAc})_3$	337 €

Figure 1

²Nicolau, C. K.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, 41, 1668-1698. 8112. ¹⁵Chackalamannil, S.; Doller, D.; Eagen, K. *Tetrahedron Lett.* **2002**, 43, 5101–5103. ¹⁶Ozawa, T.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, 13, 5390-5393 ¹⁷Kocsis, L. S.; Kagalwala, H., N., Mutto, S., Godugu, B., Bernhard, S., Tantillo, D., J., Brummond, K., M. J. *Org. Chem.* **2015**, 80, 11686–11698. ¹⁸Mun, H. J.; Seong, E. Y.; Ahn, K. H.; Kang, E. J. *J. Org. Chem.* **2018**, 83, 1196 -1203. ¹⁹Chen, X.; Zhong, C.; Lu, Y.; Yao, M.; Guan, Z.; Chen, C.; Zhu, H.; Luo, Z.; Zhang, Y. *Chem. Commun.* **2021**, 57, 5155. ²⁰For a selection of mechanistic discussions, see: (a) Houk, K. N.; Liu, F.; Yang, Z.; Seeman, J. I. *Evolution of the Diels–Alder Reaction Mechanism since the 1930s: Woodward, Houk with Woodward, and the Influence of Computational Chemistry on Understanding Cycloadditions.* *Angew. Chem., Int. Ed.* **2021**, 60, 12660. (b) Lording, W. J.; Fallon, T.; Sherburn, M. S.; Paddon-Row, M. N. *The simplest Diels–Alder reactions are not endo-selective.* *Chem. Sci.* **2020**, 11, 11915. (c) Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Hoi Hong Li, W.; Daoust, K. J.; Boddington Bovee, L.; Di Rico, K. J.; Johnson, R. P. *Concerted vs Stepwise Mechanisms in Dehydro-Diels–Alder Reactions.* *J. Org. Chem.* **2011**, 76, 9320. (d) Beno, B. R.; Houk, K. N.; Singleton, D. A. *Synchronous or Asynchronous? An “Experimental” Transition State from a Direct Comparison of Experimental and Theoretical Kinetic Isotope Effects for a Diels–Alder Reaction.* *J. Am. Chem. Soc.* **1996**, 118, 9984. ²¹For a selection of reviews, see: (a) Fluegel, L. L.; Hoye, T. R. *Hexadehydro-Diels–Alder Reaction: Benzyne Generation via Cycloisomerization of Tethered Triynes.* *Chem. Rev.* **2021**, 121, 2413. (b) Desimoni, G.; Faita, G.; Quadrelli, P. *Forty Years after “Heterodiene Syntheses with α,β -Unsaturated Carbonyl Compounds”:* *Enantioselective Syntheses of 3,4-Dihydropyran Derivatives.* *Chem. Rev.* **2018**, 118, 2080. (c) Oliveira, B. L.; Guo, Z.; Bernardes, G. J. L. *Inverse electron demand Diels–Alder reactions in chemical biology.* *Chem. Soc. Rev.* **2017**, 46, 4895. (d) Klas, K.; Tsukamoto, S.; Sherman, D. H.; Williams, R. M. *Natural Diels–Alderase: Elusive and Irresistible.* *J. Org. Chem.* **2015**, 80, 11672 ²²(a)Brummond, K. M.; Kocsis, L. S. *Intramolecular DidehydroDiels–Alder Reaction and Its Impact on the Structure–Function Properties of Environmentally Sensitive Fluorophores.* *Acc. Chem. Res.* **2015**, 48, 2320. (b) Benedetti, E.; Kocsis, L. S.; Brummond, K. M. *Synthesis and Photophysical Properties of a Series of Cyclopenta[b]naphthalene Solvatochromic Fluorophores.* *J. Am. Chem. Soc.* **2012**, 134, 12418.

Results and discussion

We discovered this reaction by treating propargyl alcohol **1a** with MnO₂. The reaction provided the compound **2a**, We observed the formation of a new aromatic ring through the functionalization of an aromatic C-H bond (Table 1).



Entry ^a	Solvent	T°C	MnO ₂ (equiv.)	Conc. of 1a (M)	Yield of 2a (%) ^b
1	DCE	25	4	0.12	20
2	DCE	50	10	0.12	28
3	DCE	50	40	0.12	45
4	Toluene	50	40	0.12	29
5	MTBE	50	40	0.12	15
6	CHCl ₃	50	40	0.12	44
7	CH ₂ Cl ₂	40	40	0.12	38
8	CH ₂ Cl ₂	25	40	0.12	35
9	CH ₂ Cl ₂	25	40	0.025	51
10	CH ₂ Cl ₂	25	40	0.0125	58
11	CH ₂ Cl ₂	25	40	0.0083	68

Table 1. Optimization of reaction conditions. ^a: 0.25 mmol of **1a**, X equiv. Of MnO₂, stirred under air overnight, ^b: isolated yield.

In a first experiment, 4 equiv. of MnO₂ were used for consuming **1a**. The reaction was conducted in dichloroethane. The yield of the desired product was 20% (entry 1) with cinnamaldehyde as side product (15%) and uncomplete conversion of the starting material **1a** (60% of recovery). 10 equiv of the oxide and temperature at 50°C increased slightly the yield (28%, entry 2). A further increment to 40 equiv. allowed the isolation of **2a** in 45% (entry 3). Replacement of DCE with toluene and MTBE proved detrimental (entry 4-5). Then we decided to replace DCE with DCM and performed the reaction at ambient temperature (entry 7-8). Lowering the concentration of **1a** had a good impact to the yield (entry 9-10). A further decrease to 0.0083 M, allowed the isolation of **2a** in 63% (entry 11). Finally, we tried to recover the MnO₂ previously used in another reaction and reused it. We retrieved a mass corresponding to the 91% of the oxide. However its use afforded **2a** in 34 % and uncomplete conversion of **1a**.

With the conditions in hands, we extended the feasibility of this method to a series of styrylnols, in order to afford their corresponding tricycles (Figure 2). Several substrates worked well. In substrates **1b**, **1c** and **1d** the aromatic ring was replaced with extended aromatic rings such as 1-naphtyl, 2-naphtyl and 9-anthracene. Chloride (substrate 54%, **2e**) and bromide (64 %, **2p**) were tolerated and both tricycles could smoothly undergo a Buckwald-Hartwig reactions with secondary amines affording their corresponding fluorescent probes.²² Enynol **1f**, which has a methoxy group, gave two regioisomers of **2**. A substrate with a trifluoromethyl group gave **2g** as a single isomer (17%). The presence of a monosubstituted propargyl moiety in substrate **1j** decreased dramatically the yield of the desired product (31%, **2j**). Replacement of oxygen with nitrogen into the tether did not increase the yield of **2h** (48%). The presence of a methyl group in *ortho*-position to the vinyl group in substrate **1i** diminished the yield of the tricycle (23%, **2i**). Then we investigated the reactivity of substituted styrylnols on their propargyl moiety. This feature enhanced enormously the yield of **2n** (90%). This reaction was scaled up to 1 mmol, albeit with a diminished yield (64%). The reaction performed well with substrates **1k**, **1l** and **1m** (80, 71 and 75%, respectively, Scheme 2). A MeO- group in *ortho* position to the vinyl group in substrate **1o** gave access the corresponding cycle in 70%. Enynols with a *meta*-substituted aromatic ring afforded two different regioisomers of **2q** and **2r**. In this case, the presence of a strong donating or withdrawing group doesn't have particular impact on the total yield (90% for **1q** and 80% for **1r**). Replacing the aromatic ring with a thiophene, we obtained the cycle **2s** in 41 % yield. Enynols featuring a secondary alcoholic function gave low yields: 9% for **2t** and 8 % for **2u**. In these reactions the main product was the linear ketone. With the addition of two methyl groups at the propargyl moiety in **1v** the yield of the cycle enhanced dramatically to 87%.

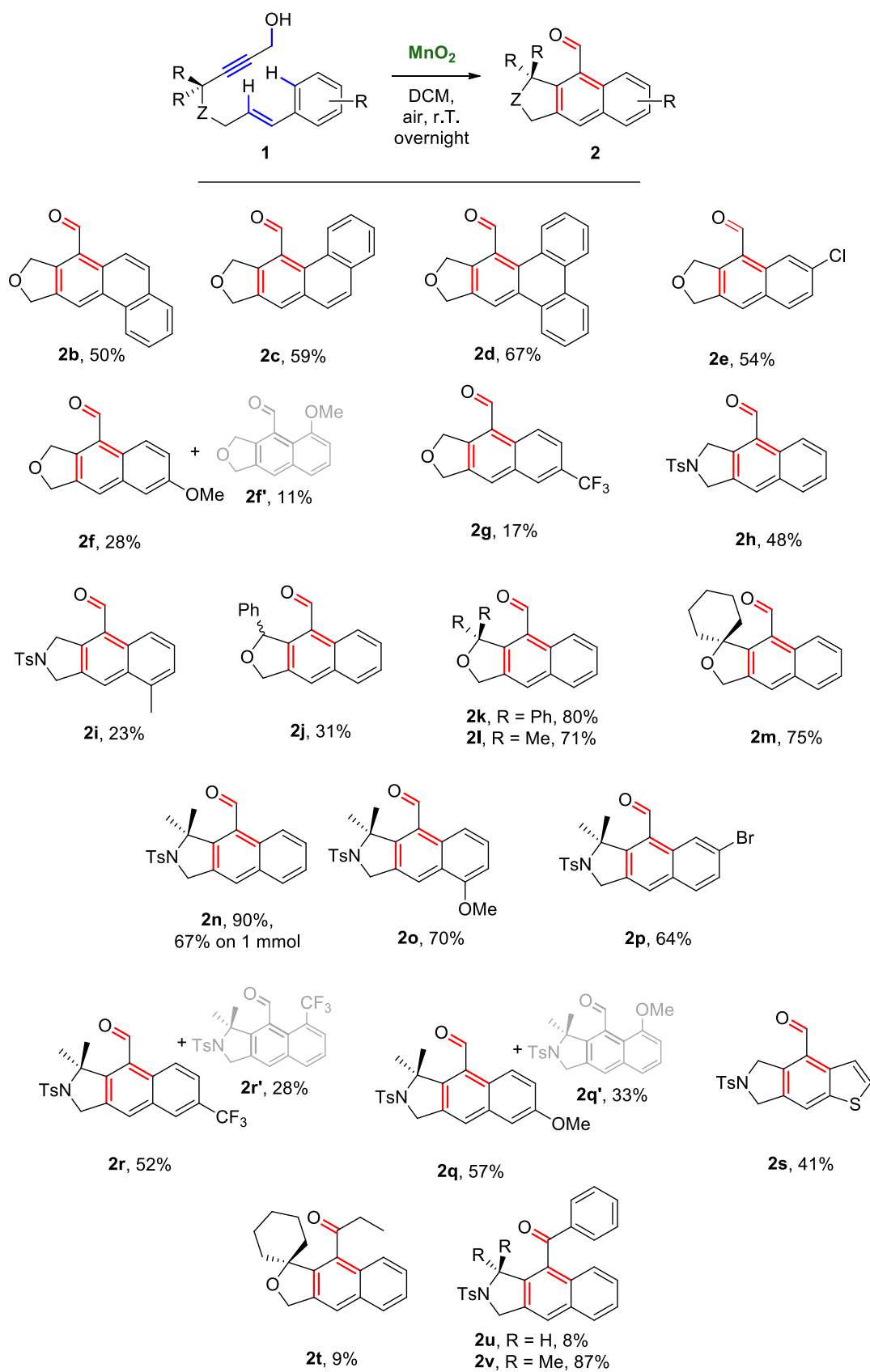


Figure 2. Scope of the method, isolated yields, conditions as Table 1, entry 11.

These last experiments highlighted the strong Thorpe-Ingold effect occurring in the present cyclisation. Furthermore disubstitution at the propargylic moiety, on average, seems to hinder the formation of cinnamaldehyde, the main byproduct of the reaction. We assumed that its formation derived from the homolytic cleavage of a propargylic C-H bond, which could be made by a manganese species. The resulting C-centered radical would undergo β -fragmentation to produce a stabilized (aryl)allyl radical, which at the end produces cinnamaldehyde in the presence of air (Figure 3). This assumption is consistent with the low yield of **2j**, which has a propargylic C-H bond that is prone to undergo homolysis.

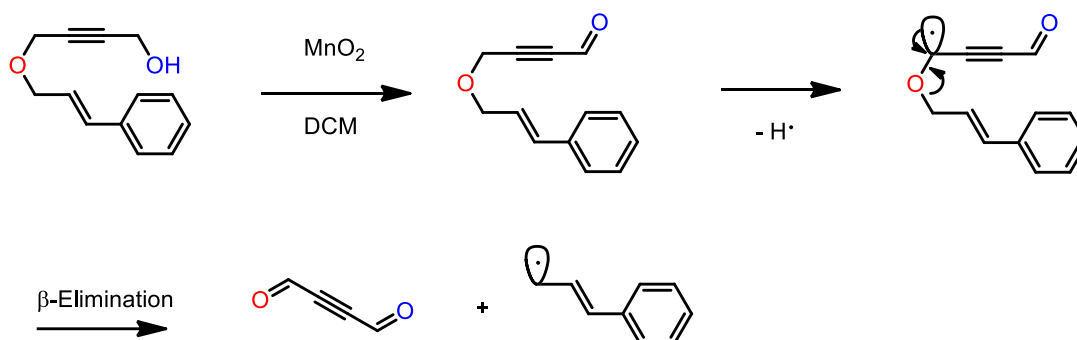
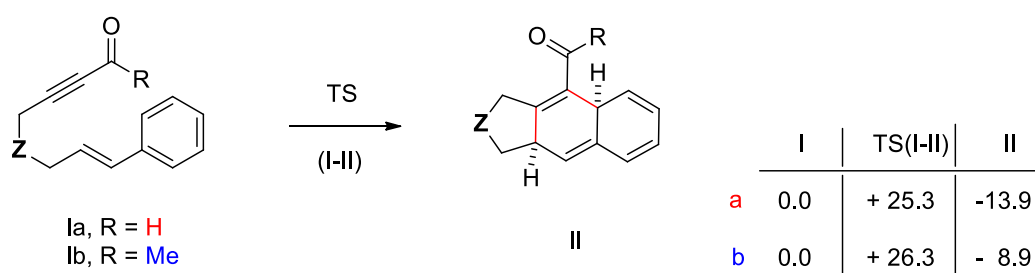


Figure 3. The homolytic cleavage of the propargylic C-H bond which produces cinnamaldehyde

With the results collected from the scope, we proposed a hypothetical reaction mechanism. Substrate **1**, undergoing oxidation promoted by MnO_2 , generates an aldehyde. Then, the ynal would undergo a Diels-Alder-cyclization involving a manganese species via carbonyl coordination. The resulting dihydronaphthalene would eventually give **2** probably thanks to a second equivalent of MnO_2 or in the presence of air via *syn* elimination of H_2 or oxidative dehydrogenation.

According to the literature, the Diels-Alder reaction should have only one transition state (TS).¹⁵⁻²¹ Compared to general Diels-Alder reactions and experiments, this cyclisation might have a lower energy cost. DFT calculations were carried out in order to understand the reaction mechanism. Without a Mn species, one single transition state occurred during the cyclization of **1a** (Figure 4, a). This TS features a remarkable energetic barrier (between +23 and +27 kcal/mol in ΔG for **1a**). Similar outcomes were seen when ketone **1b** was used. These results are comparable with experiments in which thermal conditions are required.^{17,18} In the presence of $\text{Mn}(\text{OH})_2$, the coproduct of the oxidation of **1**, the energy profile is different (Figure 4, b). Whereas in the previous study we were able to notice a concerted mechanism, in this case the stepwise process seems to occur. The energetic barriers for TS(I-III) and TS(III-II) are at +14.6 and +16.6 kcal/mol in ΔG (Figure 4b) using DCM as solvent. Similar outcomes were seen for MnOOH , the manganese (III) specie.

a) concerted, uncatalyzed



b) stepwise, $^6\text{Mn}(\text{OH})_2$ - and $^5\text{MnOOH}$ - catalyzed

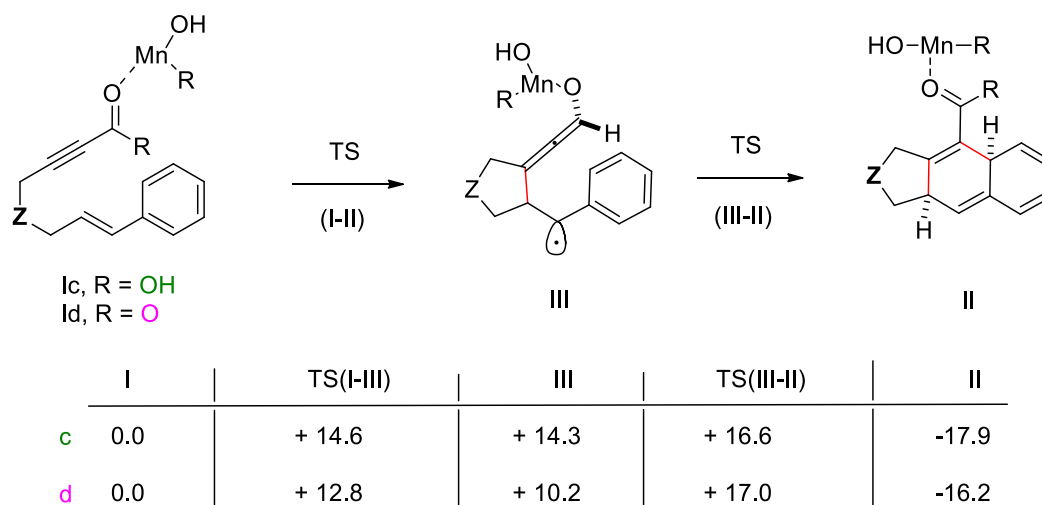


Figure 4. Concerted vs stepwise dearomative cyclizations

In order to demonstrate experimentally the reaction mechanism, we prepared **3u** and treated it with three different manganese compounds: MnO_2 , $\text{Mn}(\text{OAc})_3$, MnI_2 (1.5 equiv.) In each compound manganese has a different oxidation number, IV, III and II, respectively. The aim of these experiments was to demonstrate which manganese species are involved during the annulation. The result of these tests reported that ynal **3u** treated with MnI_2 afforded its cycle in 27% in contrast with the 4% with MnO_2 and 6 % with $\text{Mn}(\text{III})\text{OAc}$ (Figure 5).

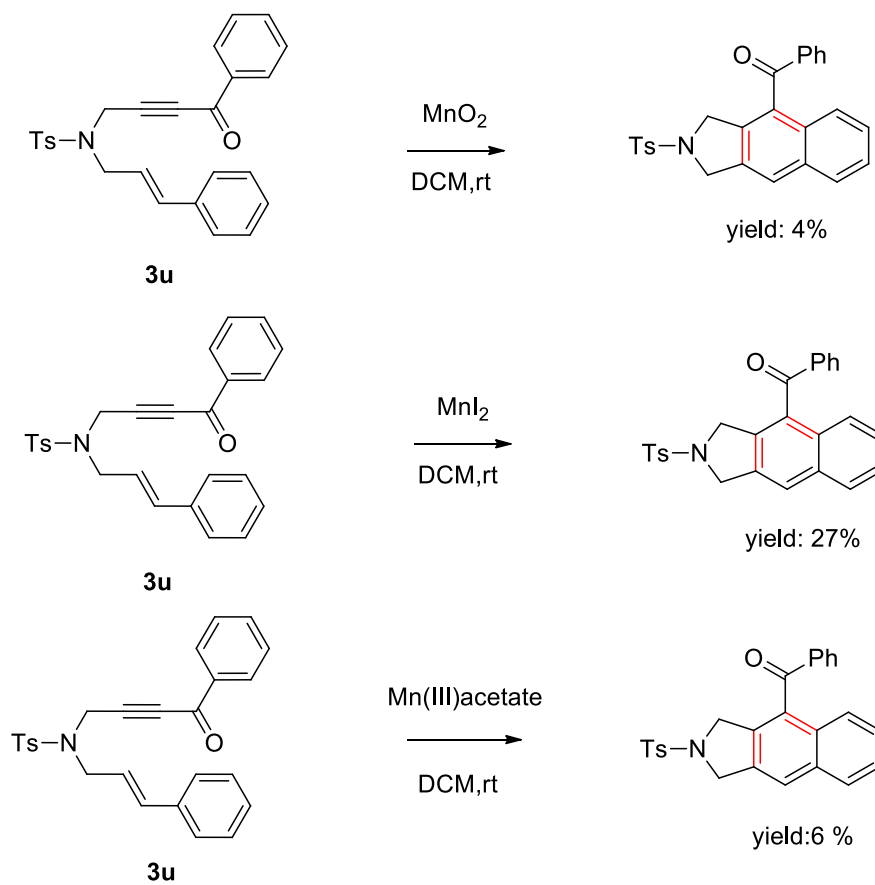


Figure 5. Attempted Cyclisation of Styrylone **3u**

These experiments suggested that after oxidation of enynol **1**, the manganese (II) is likely the catalyst of the cyclization. We can now summarize the reaction mechanism (Figure 5). Oxidation promoted by MnO_2 allows the formation of the ynal **A**. Afterwards this intermediate undergoes a first cyclisation via Mn (II)-carbonyl coordination affording product **B**. Then **B** undergoes a second cyclisation providing **C** which finally rearranged to the desired product **2** via H_2 elimination

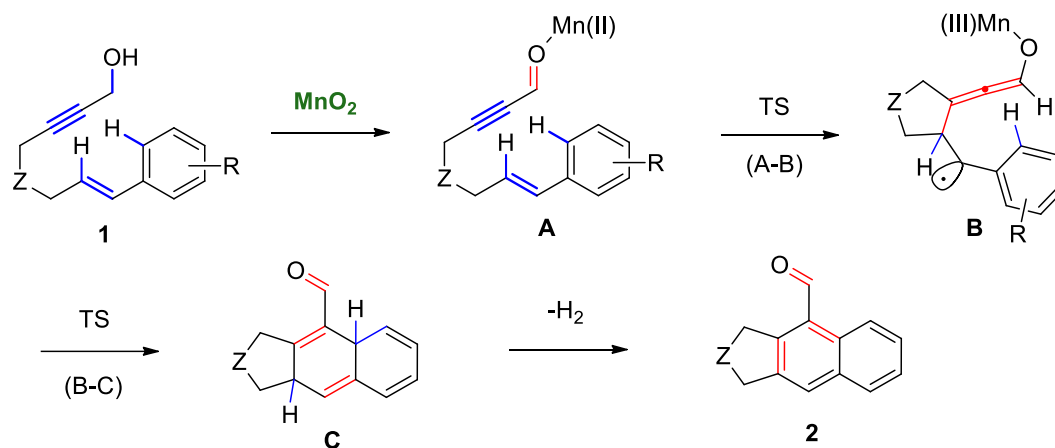


Figure 6. Reaction mechanism

Conclusion

We described a synthetic method in which styrylnols are involved in a novel cascade promoted by MnO_2 . This technique makes use of the cheapest source of manganese and operates at ambient temperature. The reactions produced a wide range of naphthalene derivatives and it displays three different steps: substrate oxidation, cyclization, and aromatization. A catalytic stepwise Diels-Alder process is likely responsible for the annulation, and because of its energy convenience, it may be useful for promoting other dearomative transformations.

Experimental section

General Remarks

Unless otherwise noted, reagents and solvents were purchased from commercial sources and used as received without further purification. Manganese dioxide used for cyclizations was in powder form, synthetic grade (>90%). Four different commercially available samples provided comparable results on the model substrate, while the use of bigger aggregates, such as pellets, provided lower conversion of the starting material. Dry solvents used for the preparation of substrates were prepared by passing them through alumina columns using an Inert® systems and were stored under nitrogen. Chromatographic purifications were performed under gradient using a Combiflash® system and prepacked disposable silica cartridges or through isocratic flash chromatography using commercial 60 Å silica gel. All reactions that required heating were performed with the use of high-vacuum grade silicon oil as heating transfer agent. ¹H and ¹³C NMR spectra were recorded at 300 K on a Bruker 400 MHz or Bruker 300 MHz spectrometer using solvents as internal standards (7.26 ppm for ¹H NMR and 77.16 ppm for ¹³C NMR for CDCl₃). ¹⁹F NMR spectra were recorded at 300 K on a Varian 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. Reported assignments were based on COSY, HSQC and HMBC correlation experiments. LC-MS were recorded on an Agilent LQ Mass Spectrometer (ESI source). High-resolution mass analyses were recorded on a LTQ ORBITRAP XL Thermo Mass Spectrometer (Electrospray source).

Computational methods

Calculations were performed at the DFT level using the Gaussian 09 suite.²³ The geometries of all species were optimized without constraints under a generalized gradient approximation using the M06 hybrid functional defined by Zhao and Truhlar.²⁴ Optimizations were carried out using the Def2-SVP(d) set defined by Weigand and Ahlrichs.²⁵ On Def2-SVP(d) optimized geometries, complete re-optimization was performed employing a more refined triple- ζ basis set, namely the Def2-TZVP(d) set defined by Weigand and Ahlrichs.²⁶ The gas-phase structures were then freely reoptimized using dichloromethane as an implicit solvent as implemented in Gaussian 09 through the CPCM approach.²⁷ The key steps were also tested at the M06-L and at the M06-2X level to exclude significant biases resulting from functionals. Overall, no mayor differences emerged among these tested models. The starting approximate geometries for transition states (TS) were obtained through scans of the relative reaction coordinate starting from the corresponding reagents. Transition states were identified by the presence of a single imaginary frequency in the Hessian matrix, corresponding to the vibration along the reaction coordinate linking the reactant and the product. XYZ coordinates and a comprehensive table in atomic units including the unique imaginary IR frequency of each transition state are presented in the dedicated section at the end of this document. A table presenting all calculated values for structures optimized at various levels follows hereafter, including tests on the lowest-energy multiplicities of Mn(II) and Mn(III) complexes, and the replacement of Mn(O)OH with Mn(OAc)₃ as a representative Mn(III) derivative. As mentioned in the main article, this data parallels the main trend shown by results calculated at the M06/Def2-TZVP level. Conformational analyses on the most stable intermediate was carried out on the basis of informed guesses by testing three other different conformers of the model ynal **1a**, which is the one that can undergo the Diels-Alder cyclization. In analogy with literature findings on similar substrates, including reports by our group (see refs 11 of the

main article), all of the different conformers were nearly degenerate in energy (Figure S1), differences remaining below the 1 kcal/mol in ΔG . This result indicates that the different conformers of the substrate are likely in a dynamic equilibrium, which can be shifted depending on the most favourable energetic manifold of the reaction. It is worth noting that present approach based on a simplified conformational analysis is often sufficient for small molecular systems, as it is the case of present study, while it could lead to significant errors for larger ones, such as complexes involving more than 100 atoms.²⁸ Upon the first TS, intermediates **III** have very limited conformation flexibility as a result of their cyclic structure. Final intermediates **II** follow suit, being fused tricycles. This is witnessed by decreasing entropic values throughout the series (see section 8). No additional conformational analyses were thus carried out on these species.

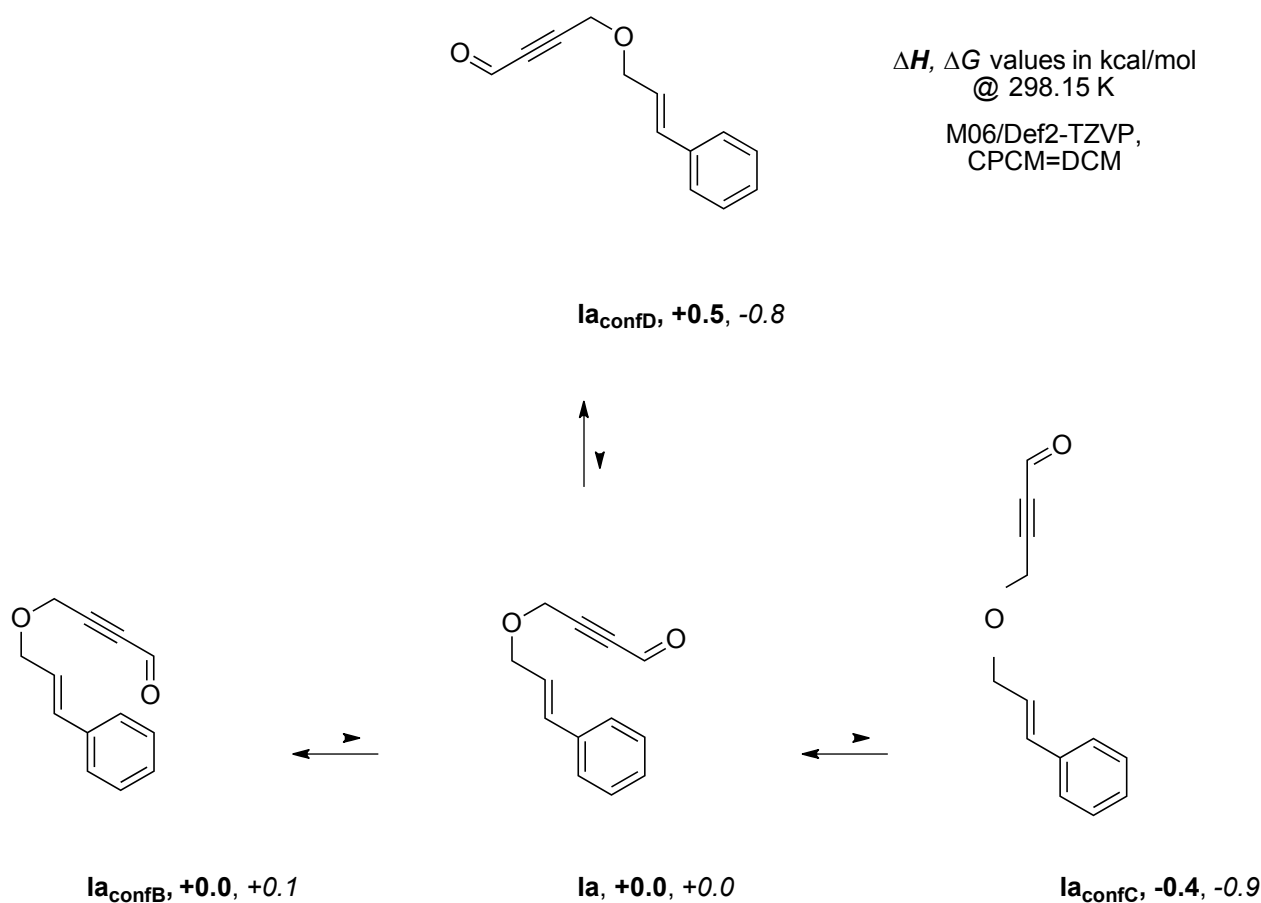


Figure S1. Modeled conformers of enynal **Ia**.

A direct comparison of the catalytic vs thermal pathway requires a common reference point, such as enynal **Ia**. For reactions of systems **c-h** in the main article, we preferred to plot separately each catalytic reaction to provide a more straightforward representation of the analogies between the different catalysts (paramagnetic manganese species, iminium catalysis, diamagnetic Lewis acids based on early transition metals, late transition metals and main-group elements). Hereafter, Figure S2 presents the comparison of the Lewis acids pathways (left) referenced to ynal **Ia** (thermal reaction on the right).

As can be readily observed, both relative barriers described in the main article as well as absolute maxima for all of the catalysed reactions lie below the TS of the thermal process.

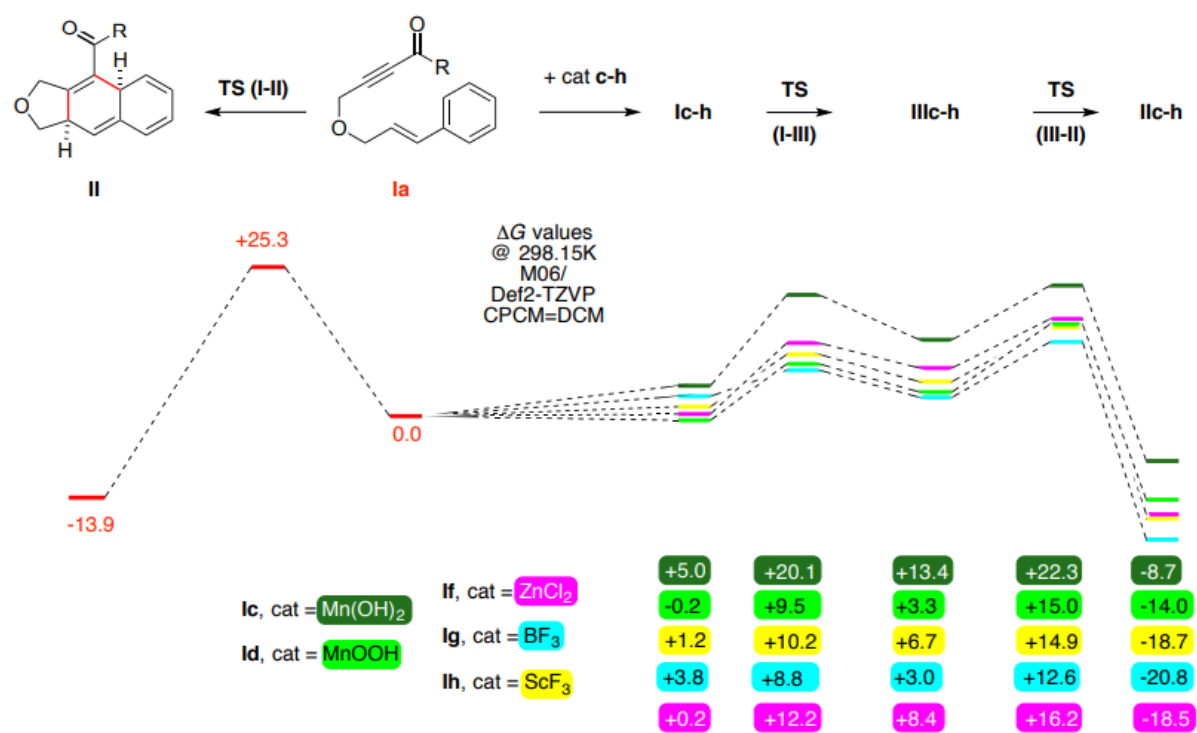


Figure S2. Comparison of catalytic vs thermal reactions referenced to ynal Ia.

M06/Def2-SVP

	ΔH (kcal/mol)	ΔS (cal/K*mol)	ΔG (kcal/mol @298.15)
Ia			
TS (I-II)a	20.331	-13.243	24.28
IIa	-26.782	-18.075	-21.39
Ib			
TS (I-II)b	22.569	-8.963	25.24
IIb	-20.598	-14.097	-16.39
Ie			
TS (I-III)e	1.901	-4.760	3.32
IIIe	-2.963	-1.963	-2.38
TS (III-II)e	3.549	-6.989	5.63
IIe	-22.664	-8.916	-20.01
¹ Id	0.000	0.000	0.00
⁵ Id	-45.727	7.349	-47.92
⁴ Ic	0.000	0.000	0.00
² Ic	39.278	3.423	38.26
⁶ Ic	-10.879	9.632	-13.75
⁴ Ic			
⁴ TS (I-III)c	6.950	-2.033	7.56
⁴ IIc	-11.884	-4.927	-10.41
⁴ TS (III-II)c	7.528	-6.404	9.44
⁴ IIc	-13.360	0.107	-13.39
⁶ Ic			
⁶ TS (I-III)c	2.638	-10.682	5.82
⁶ IIc	0.325	-11.696	3.81
⁶ TS (III-II)c	8.552	-11.583	12.01
⁶ IIc	-27.377	-7.579	-25.12
Id			
TS (I-III)d	13.165	-6.411	15.08
IIId	-2.735	-6.115	-0.91
TS (III-II)d	13.721	-10.124	16.74
IIId	-19.379	-6.066	-17.57
If			
TS (I-III)f	9.831	-6.502	11.77
IIIIf	6.852	-5.643	8.53

TS (III-II)f	14.152	-8.533	16.70
IIf	-21.497	-5.361	-19.90

Ig			
TS (I-III)g	10.112	-5.777	11.83
IIIg	5.759	-6.527	7.71
TS (III-II)g	11.053	-9.738	13.96
Ilg	-27.030	-7.045	-24.93

Ih			
TS (I-III)h	7.214	-9.656	10.09
IIIh	5.351	-4.099	6.57
TS (III-II)h	9.707	-8.165	12.14
Iih	-25.060	-5.790	-23.33

M06-L/Def2-TZVP CPCM=dcM

Ia			
TS (I-II)a	18.852	-15.743	23.55
Ila	-15.220	-18.942	-9.57

Ib			
TS (I-II)b	21.213	-13.113	25.12
Ilb	-8.865	-16.879	-3.83

Ie			
TS (I-III)e	4.327	-3.285	5.31
IIIe	1.217	-1.139	1.56
TS (III-II)e	8.950	-8.474	11.48
Ile	-14.630	-9.488	-11.80

Ic			
TS (I-III)c	12.708	-7.989	15.09
IIIc	4.413	-13.277	8.37
TS (III-II)c	13.746	-12.000	17.32
Iic	-17.010	-11.120	-13.69

Id			
TS (I-III)d	8.854	-2.913	9.72
IIId	1.831	-5.500	3.47
TS (III-II)d	13.331	-6.229	15.19
IId	-16.140	-7.754	-13.83

I -⁵Mn(OAc)₃			
TS (I-III) -⁵Mn(OAc)₃	7.183	-7.808	9.51
III -⁵Mn(OAc)₃	6.994	-8.411	9.50
TS (III-II) -⁵Mn(OAc)₃	11.654	-9.219	14.40
II -⁵Mn(OAc)₃	-17.731	-8.545	-15.18

Additional control experiments

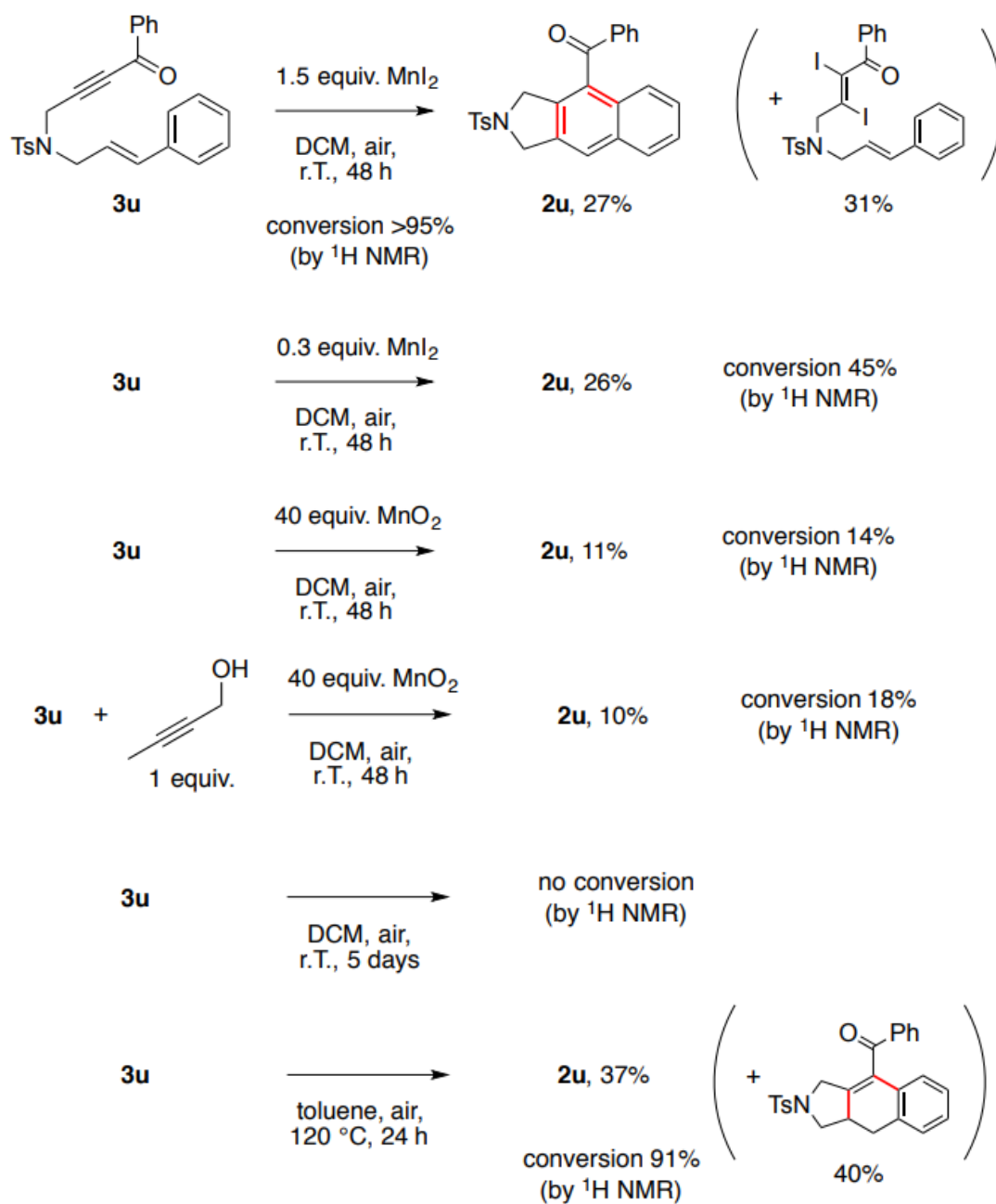
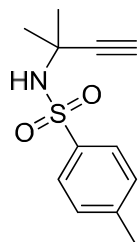


Figure S3. Additional details on reactions of ynone **3u**.

²³Gaussian 09, Revision A.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**. ²⁴Zhao, Y.; Truhlar, D. G. *Theor. Chem. Account* **2008**, 120, 215. ²⁵(a) Weigen, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* 2005, 7, 3297; (b) Andrae, D.; Haeussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Theor. Chim. Acta* **1990**, 77, 123; (c) Peterson, K. A.; Figgen, D.; Goll, E.; Stoll, H.; Dolg, M. *J. Chem. Phys.* **2003**, 119, 11113. ²⁶(a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, 102, 1995; (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, 24, 669; (c) Klamt, A.; Schuurmann, G. *J. Chem. Soc., Perkin Trans* **1993**, 2, 799; (d) Schäfer, A.; Klamt, A.; Sattel, D.; Lohrenz, J. C. W.; Eckert, F. *Phys. Chem. Chem. Phys.* **2000**, 2, 2187. ²⁷Besora, M.; Braga, A. A. C.; Ujaque, G.; Maseras, F.; Lledós, A. *Theor. Chem. Acc.* **2011**, 128, 639.

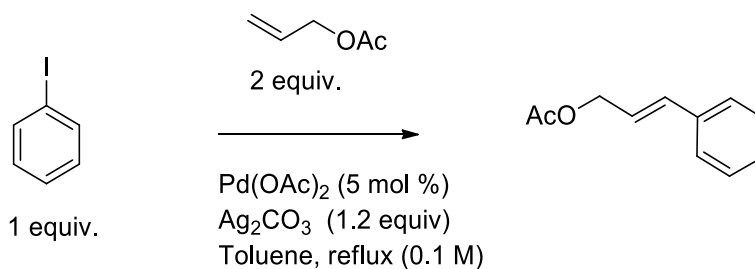
Synthesis of reagents

Synthesis of 4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide



The reaction was carried out following a literature procedure.²⁸ To a mixture of 2-methylbut-3-yn-2-amine (1.7 ml, 27.2 mmol, 1 equiv.) and triethylamine (4.2 ml, 30 mmol, 1.1 equiv.) in DCM (8 mL) cooled at 0 °C was added dropwise a solution of tosyl chloride (5.7 g, 30 mmol, 1.1 equiv.) in DCM (60 ml). The mixture was allowed to warm to room temperature and kept under stirring for 5 hours. Afterwards, 30 ml of water were added and the mixture was extracted with DCM (3 x 50 mL). The combined organic phases were washed with saturated brine and then dried over anhydrous NaSO₄. The crude product was concentrated under reduced pressure, solubilized with ethyl acetate and the desired product was recovered by crystallization achieved by the addition of hexane (96%, 5.5 g, 23mmol).

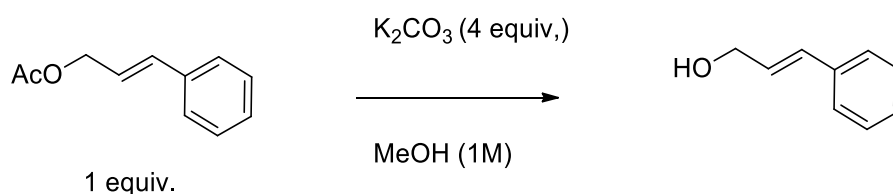
General procedure for Heck couplings



The reaction was carried out following a literature procedure.²⁹ To a mixture of Pd(OAc)₂ (5 mol%) and Ag₂CO₃ (typically 6 mmol, 1.2 equiv.) in toluene (0.1 M) were sequentially added the desired aryl iodide (typically 5 mmol, 1 equiv.) and allylic acetate (typically 10 mmol, 2 equiv.). The resulting mixture was heated to reflux until complete conversion of the iodide, which was monitored by TLC (6 hours). The mixture was filtered over celite, concentrated under reduced pressure and then carefully purified by flash chromatography (isocratic *n*-Hexane/EtOAc 9:1) to afford the desired product.

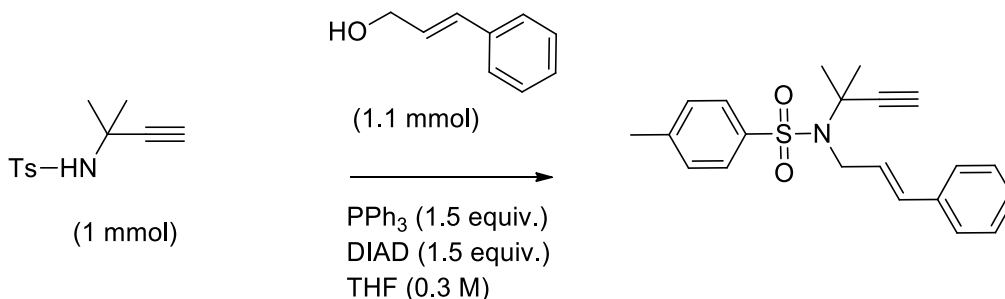
²⁸ Benedetti, E.; Simonneau, A.; Hours, A.; Amouri, H.; Penoni, A.; Palmisano, G.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. *Adv. Synth. Catal.* **2011**, 353, 1908. S156. ²⁹ Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem. Int. Ed.* **2008**, 47, 4729

General procedure for the hydrolysis of arylallylacetates



The reaction was carried out following a procedure reported in the literature.³⁰ In a round bottom flask equipped with a magnetic stirring bar, the desired arylallylacetate (typically 4 mmol, 1 equiv.) was dissolved in methanol (1 M) and K_2CO_3 (typically 16 mmol, 4 equiv.) was eventually added. The resulting mixture was stirred at room temperature overnight. The mixture was quenched with the addition of water (10 ml) and then extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with saturated brine and then dried over anhydrous Na_2SO_4 . The crude was concentrated under reduced pressure and purified by flash chromatography (isocratic *n*-Hexane/EtOAc 8:2) to afford the desired product.

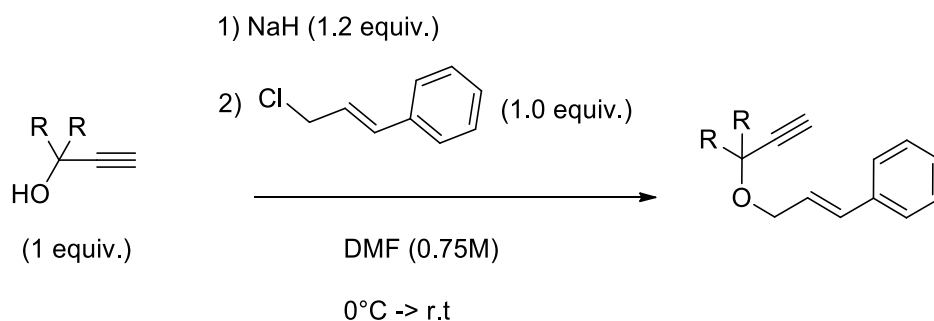
General procedure for the synthesis of enynes (GP-1)



PPh_3 (typically 1.5 mmol, 1.5 equiv.) and 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (typically 1 mmol, 1.0 equiv.) were sequentially added to a solution of the desired allyl alcohol (typically 1.1 mmol, 1.1 equiv.) in dry THF (0.3 M). The mixture was cooled to 0 °C and DIAD (typically 1.5 mmol, 1.5 equiv.) was added dropwise. The resulting mixture was stirred at room temperature until complete conversion of the sulfonamide, which was monitored by TLC. Hence, the solution was concentrated under reduced pressure and purified by flash chromatography (isocratic *n*-Hexane/EtOAc 95:5) to afford the desired product.

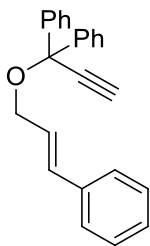
³⁰ Malkov, A. V.; Gouriou, L.; Lloyd-Jones, G. C.; Stry, I.; Langer, V.; Spoor, P.; Vinader, V.; Kocovsky, P. *Chem. Eur. J.* **2006**, 12, 6910.

General procedure for the synthesis of enynes (GP-2)



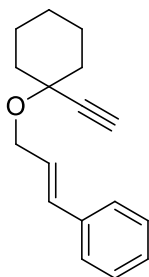
To a suspension of NaH (typically 2.4 mmol, 1.2 equiv., 60% w/w dispersion in mineral oil in dry DMF (0.75 M), the desired propargyl alcohol (typically 2 mmol, 1.0 equiv.) was added dropwise at 0 °C. The mixture was kept under stirring for 15 minutes upon termination of hydrogen evolution. Then, the desired allyl halide (typically 2 mmol, 1.0 equiv.) was added and the resulting mixture was allowed to warm up to room temperature. Stirring was continued for 2 hours. The reaction was quenched with water (10 ml) and diluted with ethyl acetate (20 ml). The organic layer was washed with a saturated solution of sodium carbonate and brine, dried over anhydrous Na₂SO₄, filtered, concentrated and then purified by column chromatography (isocratic *n*-Hexane/EtOAc 9:1) to afford the desired product.

(E)-(1-(cinnamyloxy)prop-2-yne-1,1-diyl)dibenzene (E1)



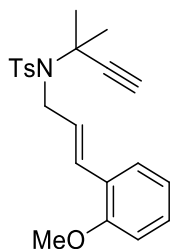
E1 was isolated following procedure **GP-2** using 1,1-diphenylprop-2-yn-1-ol (1000 mg, 4.8 mmol) and (E)-(3-bromoprop-1-en-1-yl)benzene (1135 mg, 5.8 mmol). Purification by column chromatography (isocratic *n*-Hexane/EtOAc 9:1) afforded **E1** (90%, 1410 mg, 4.35 mmol) as a whitesolid. **¹H NMR** (400 MHz, CDCl₃) δ = 7.67 (d, *J* = 7.1 Hz, 3H), 7.44 (d, *J* = 7.0 Hz, 2H), 7.41-7.27 (m, 10H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.41 (dt, *J* = 15.9, 5.8 Hz, 1H), 4.27 (dd, *J* = 5.8, 1.6 Hz, 2H), 2.97 (s, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.2 (2Cq), 137.1 (Cq), 131.7 (CH), 128.6 (2CH), 128.4 (4CH), 127.9 (2CH), 127.6 (CH), 126.8 (4CH), 126.6 (2CH), 126.4 (CH), 83.5 (Cq), 80.3 (Cq), 77.9 (CH), 65.9 (CH₂). **ESI-MS** calculated for C₂₄H₂₁O [M+H]⁺ 325.16, found 325.10. **ESI-HRMS** calculated for C₂₄H₂₁O[M+H]⁺ 325.1587 found 325.1597.

(E)-(3-((1-ethynylcyclohexyl)oxy)prop-1-en-1-yl)benzene (E2)



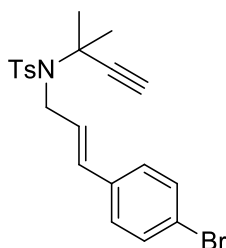
E2 was isolated following procedure **GP-2** using 1-ethynylcyclohexanol (1000 mg, 8.0 mmol) and (E)-(3-bromoprop-1-en-1-yl)benzene (1904 mg, 9.7 mmol). Purification by column chromatography (isocratic *n*-Hexane/EtOAc 9:1) afforded **E2** (94%, 1804 mg, 7.5 mmol) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.41 (d, *J* = 6.8 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.26-7.21 (m, 1H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.36 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.32 (dd, *J* = 6.0, 1.5 Hz, 2H), 2.52 (s, 1H), 2.04 - 1.94 (m, 2H), 1.76-1.52 (m, 7H), 1.39-1.27 (m, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 137.1 (Cq), 131.7 (CH), 128.6 (2CH), 127.5 (CH), 127.0 (CH), 126.6 (2CH), 85.3 (Cq), 74.0 (CH), 73.9 (Cq), 64.3 (CH₂), 37.3 (4CH), 25.5 (2CH), 22.8 (4CH). **ESI-MS** calculated for C₁₇H₂₁O [M+H]⁺ 241.16, found 241.20. **ESI-HRMS** calculated for C₁₇H₂₁O [M+H]⁺ 241.1587, found 241.1580.

(E)-N-(3-(2-methoxyphenyl)allyl)-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (E3)



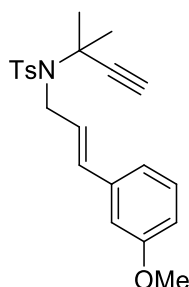
E3 was isolated following procedure **GP-1** using 4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (474.7 mg, 2 mmol) and (E)-3-(2-methoxyphenyl)prop-2-en-1-ol (361.2 mg, 2.2 mmol). Purification by column chromatography (isocratic *n*-Hexane/EtOAc 95:5) afforded **E3** (37%, 287 mg, 0.75 mmol) as a colourless oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.78 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 7.4 Hz, 1H), 7.25-7.20 (m, 2H), 6.96-6.84 (m, 3H), 6.40 (dt, J = 16.2, 6.4 Hz, 1H), 4.37 (dd, J = 6.5, 1.5 Hz, 2H), 3.83 (s, 3H), 2.39 (s, 4H), 1.73 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 156.7 (Cq), 142.9 (Cq), 139.9 (Cq), 129.3 (2CH), 128.7 (CH), 128.5 (CH), 127.3 (2CH), 127.2 (CH), 126.8 (CH), 125.7 (Cq), 120.6 (CH), 110.9 (CH), 86.5 (Cq), 72.1 (CH), 56.3 (Cq), 55.5 (CH₃), 50.6 (CH₂), 30.7 (2CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₂H₂₅NNaO₃S [M+Na]⁺ 406.15, found 406.07. **ESI-HRMS** calculated for C₂₂H₂₅NNaO₃S [M+Na]⁺ 406.1447, found 406.14

(E)-N-(3-(4-bromophenyl)allyl)-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (E4)



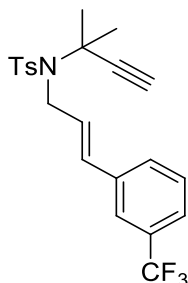
E4 was isolated following procedure **GP-1** using 4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (304 mg, 1.3 mmol) and (E)-3-(4-bromophenyl)prop-2-en-1-ol (300 mg, 1.4 mmol). Purification by column chromatography (isocratic *n*-Hexane/EtOAc 95:5) afforded **E4** (37%, 208 mg, 0.48 mmol) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.74 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.29-7.20 (m, 4H), 6.50 (d, J = 15.9 Hz, 1H), 6.36 (dt, J = 16.0, 6.2 Hz, 1H), 4.32 (d, J = 6.1, 1.3 Hz, 2H), 2.40 (s, 3H), 2.36 (s, 1H), 1.70 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.1 (Cq), 139.8 (Cq), 135.7 (Cq), 131.7 (2CH), 131.3 (CH), 129.4 (2CH), 128.8 (CH), 128.0 (2CH), 127.3 (2CH), 121.4 (Cq), 86.4 (Cq), 72.1 (CH), 56.6 (Cq), 50.1 (CH₂), 30.6 (2CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₁H₂₂⁸¹BrNNaO₂S [M+Na]⁺ 456.04, found 456.12. **ESI-HRMS** C₂₁H₂₂⁷⁹BrNNaO₂S [M+Na]⁺ 454.0447, found 454.0440.

(E)-N-(3-(3-methoxyphenyl)allyl)-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (E5)



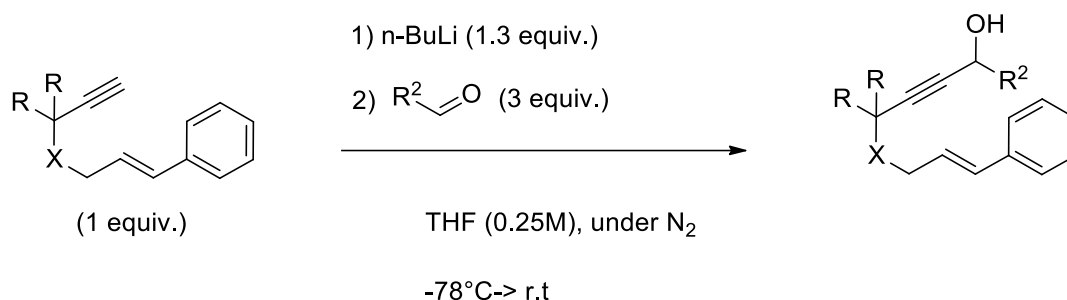
E5 was isolated following procedure **GP-1** using 4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (207 mg, 0.87 mmol) and (E)-3-(3-methoxyphenyl)prop-2-en-1-ol (157.1, 0.96 mmol). Purification by column chromatography (isocratic *n*-Hexane/EtOAc 95:5) afforded **E5** (67%, 223 mg, 0.58 mmol) as a white solid. **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.3 Hz, 2H), 7.27-7.21 (m, 3H), 6.97 (dt, J = 7.7, 1.2 Hz, 1H), 6.90 (t, J = 2.0 Hz, 1H), 6.80 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.52 (d, J = 14.4 Hz, 1H), 6.36 (dt, J = 15.9, 6.3 Hz, 1H), 4.34 (dd, J = 6.3, 1.4 Hz, 2H), 3.82 (s, 3H), 2.40 (s, 3H), 2.36 (s, 1H), 1.71 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 159.9 (Cq), 143.1 (Cq), 139.9 (Cq), 138.3 (Cq), 132.5 (CH), 129.7 (CH), 129.5 (2CH), 128.4 (CH), 127.4 (2CH), 119.3 (CH), 113.5 (CH), 111.8 (CH), 86.5 (Cq), 72.2 (CH), 56.6 (Cq), 55.4 (CH₃), 50.3 (CH₂), 30.8 (2CH₃), 21.6 (CH₃). **ESI-MS** calculated for C₂₂H₂₅NKO₃S [M+K]⁺ 422.12, found 422.27. **ESI-HRMS** calculated for C₂₂H₂₅NNaO₃S [M+Na]⁺ 406.1447, found 406.1439.

(E)-4-methyl-N-(2-methylbut-3-yn-2-yl)-N-(3-(3-(trifluoromethyl)phenyl)allyl)benzenesulfonamide (E6)



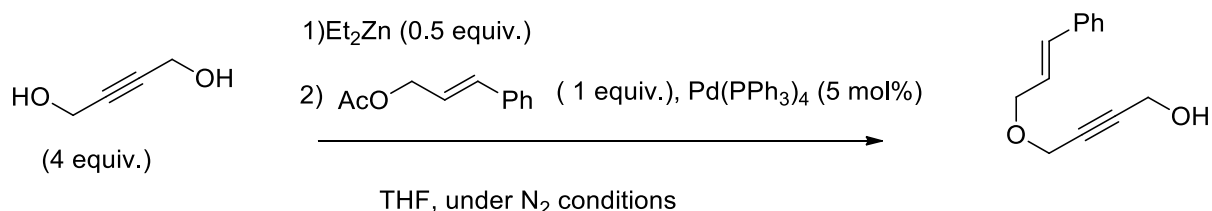
E6 was isolated following procedure **GP-1** using 4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (280 mg, 1.2 mmol) and (E)-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-ol (262 mg, 1.3 mmol). Purification by column chromatography (isocratic *n*-Hexane/EtOAc 95:5) afforded **E6** (42%, 209 mg, 0.50 mmol) as a white solid. **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.3 Hz, 2H), 7.58-7.53 (m, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.27-7.24 (m, 2H), 6.59 (d, J = 15.9 Hz, 1H), 6.43 (dt, J = 16.0, 6.0 Hz, 1H), 4.36 (dd, J = 6.1, 1.4 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 1H), 1.72 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.2 (Cq), 139.6 (Cq), 137.5 (Cq), 131.0 (CH), 130.9 (q, $J_{C,F}$ = 32 Hz, Cq), 130.0 (CH), 129.6 (CH), 129.5 (2CH), 129.1 (CH), 127.3 (2CH), 124.3 (q, $J_{C,F}$ = 272 Hz, Cq), 124.3 (q, $J_{C,F}$ = 3.8 Hz, CH), 123.3 ($J_{C,F}$ = 3.8 Hz, CH), 86.2 (Cq), 72.3 (CH), 56.6 (Cq), 50.1 (CH₂), 30.6 (2CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₂H₂₃F₃NO₂S [M+H]⁺ 422.14, found 422.07. **ESI-HRMS** calculated for C₂₂H₂₂F₃NKO₂S [M+K]⁺ 460.0955, found 460.0945. **¹⁹F NMR** (565 MHz, CDCl₃) δ = -62.6 (s).

General Procedure for synthesis of enynols (GP-3)



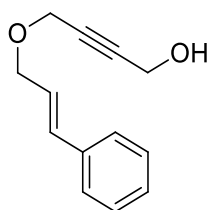
A solution of the desired enyne (typically 2 mmol, 1 equiv.) in dry THF (0.25 M) was cooled to -78 °C and a solution of BuLi (typically 2.6 mmol, 1.6 M or 2.5 M in hexane, 1.3 equiv.) was added dropwise under a N₂ atmosphere. After 1 hour, the aldehyde (typically 6 mmol, 3 equiv.) was slowly added. The mixture was allowed to warm up to room temperature and kept under stirring overnight. A saturated solution of NH₄Cl (30 mL) was added to quench the reaction and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhydrous Na₂SO₄, concentrated under reduced pressure and purified by column chromatography (eluent: gradient hexane/EtOAc).

General Procedure for synthesis of enynols (GP-4)



To a solution of but-2-yne-1,4-diol (typically 5 mmol, 4 equiv.) in THF, Et_2Zn (typically 0.63 mmol, 0.9 M in hexane, 0.5 equiv.) was added dropwise under a N_2 atmosphere. The resulting mixture was stirred until it turned cloudily white (30 min). The desired allyl acetate (typically 1.25 mmol, 1 equiv.) and $\text{Pd(PPh}_3)_4$ (5 mol%) were then added and the reaction was stirred overnight at room temperature. The resulting mixture was concentrated and carefully purified by column chromatography (eluent: gradient hexane/EtOAc).

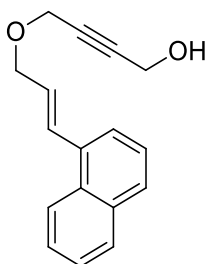
4-(cinnamyloxy)but-2-yn-1-ol (**1a**)



1a was prepared following **GP-4** and it was obtained from 1,4-butyndiol (8 g, 93 mmol) and cinnamyl chloride (6.8 mL, 48.5 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1a** (65%, 6.4 g, 31.6 mmol) as a yellow oil.

Spectroscopic data correspond to the literature.³¹ $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.41-7.37 (m, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.27-7.22 (m, 1H), 6.64 (d, J = 16.0 Hz, 1H), 6.28 (dt, J = 15.9, 6.2 Hz, 1H), 4.32 (d, J = 3.8 Hz, 2H), 4.26-4.24 (m, 4H), 2.23 (s, 1H)

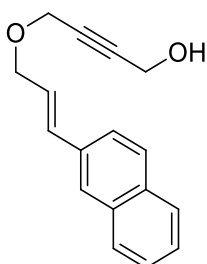
(E)-4-((3-(naphthalen-1-yl)allyl)oxy)but-2-yn-1-ol (**1b**)



1b was isolated following procedure **GP-4** using but-2-yne-1,4-diol (1040 mg, 12.0 mmol) and E)- 3-(naphthalen-1-yl)allyl acetate (550 mg, 2.4 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1b** (32%, 200 mg, 0.8 mmol) as a yellow oil. Spectroscopic data correspond to the literature.³² ¹H NMR (400 MHz, CDCl₃) δ = 8.12 (d, J = 7.9 Hz, 1H), 7.86 (dd, J = 7.9, 1.7 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.55-7.38 (m, 4H), 6.31 (dt, J = 15.7, 6.1 Hz, 1H), 4.35-4.31 (m, 6H), 2.83 (brs, 1H).

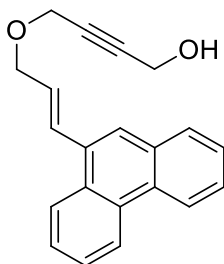
³¹M. Lanzi, T. Cañeque, L. Marchiò, R. Maggi, F. Bigi, M. Malacria and G. Maestri, *ACS Catal.*, **2018**, 8, 144. ³² C. Cecchini, G.Cera, M. Lanzi, L. Marchio; M. Malacria and G. Maestri, *Org. Chem. Front.*, **2019**, 6, 3584

E)-4-((3-(naphthalen-2-yl)allyl)oxy)but-2-yn-1-ol (**1c**)



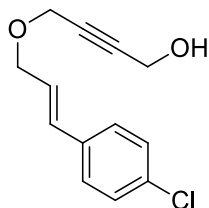
1c was isolated following procedure **GP-4** using but-2-yne-1,4-diol (732 mg, 8.5 mmol) and (E)-3-(naphthalen-2-yl)allyl acetate (385 mg, 1.7 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1c** (43%, 184 mg, 0.7 mmol) as a pale yellow wax. Spectroscopic data correspond to the literature.³² ¹H NMR (300 MHz, CDCl₃) δ = 7.82-7.77 (m, 3H), 7.74 (s, 1H), 7.60 (dd, J = 8.6, 1.7 Hz, 1H), 7.49-7.42 (m, 2H), 6.80 (d, J = 15.9 Hz, 1H), 6.40 (dt, J = 16.2, 6.1 Hz, 1H), 4.34 (s, 2H), 4.31-4.26 (m, 4H).

(E)-4-((3-(phenanthren-9-yl)allyl)oxy)but-2-yn-1-ol (**1d**)



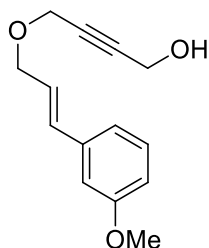
1d was isolated following procedure **GP-4** using but-2-yne-1,4-diol (402 mg, 4.7 mmol) and (E)-3-(4a,4b-dihydrophenanthren-9-yl)allyl acetate (165 mg, 0.93 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1d** (33%, 93 mg, 0.31 mmol) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.71 (d, J = 8.1 Hz, 1H), 8.64 (d, J = 7.9 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.83 (s, 1H), 7.70 -7.56 (m, 4H), 7.39 (dd, J = 15.5, 1.1 Hz, 1H), 6.4 (dt, J = 15.5, 6.0 Hz, 1H), 4.39 -4.33 (m, 6H), 2.22 (s, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ = 133.4 (Cq), 131.8 (Cq), 131.1 (CH), 130.5 (Cq), 130.4 (Cq), 130.3 (Cq), 128.8 (CH), 128.7 (CH), 126.9 (CH), 126.7 (CH), 126.7 (CH), 126.6 (CH), 125.1 (CH), 124.7 (CH), 123.1 (CH), 122.6 (CH), 85.0 (Cq), 81.8 (Cq), 70.6 (CH_2), 57.7 (CH_2), 51.2 (CH_2). **ESI-MS** calculated for $\text{C}_{21}\text{H}_{18}\text{KO}_2[\text{M}+\text{K}]^+$ 341.09 found 341.39. **ESI-HRMS** calculated for $\text{C}_{21}\text{H}_{18}\text{NaO}_2[\text{M}+\text{Na}]^+$ 325.1199 found 325.1203.

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



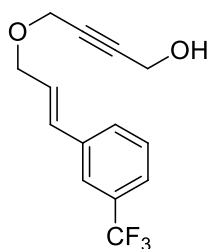
1e was isolated following procedure **GP-4** using but-2-yne-1,4-diol (851 mg, 9.9 mmol) and (*E*)-3-(4-chlorophenyl)allyl acetate (417 mg, 1.9 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1e** (58 %, 255 mg, 1.1 mmol) as a pale yellow oil. Spectroscopic data correspond to the literature.³² **¹H NMR** (400 MHz, CDCl₃) 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).

(*E*)-4-((3-(3-methoxyphenyl)allyl)oxy)but-2-yn-1-ol (1f**)**



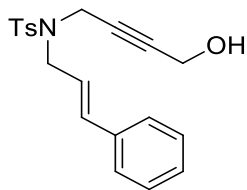
1f was isolated following the procedure **GP-4** using but-2-yne-1,4-diol (534 mg, 6.2 mmol) and (*E*)-3-(3-methoxyphenyl)allyl acetate (320 mg, 1.5 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1f** (65%, 228 mg, 0.98 mmol) as a pale yellow oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.09 (t, J = 7.9 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.80- 6.78 (m, 1H), 6.67 (dd, J = 8.3, 2.7 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 6.13 (dt, J = 15.9, 6.2 Hz, 1H), 4.18 (t, J = 1.7 Hz, 2H), 4.10-4.06 (m, 4H), 3.66 (s, 3H), 2.55 (brs, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 159.7 (Cq), 137.9 (Cq), 133.2 (CH), 129.6 (CH), 125.4 (CH), 119.2 (CH), 113.5 (CH), 111.8 (CH), 85.0 (Cq), 81.4 (Cq), 70.3 (CH₂), 57.4 (CH₂), 55.2 (CH₃), 50.9 (CH₂). **ESI-MS** calculated for C₁₄H₁₇O₃ [M+H]⁺ 233.12, found 233.12. **ESI-HRMS** calculated for C₁₄H₁₇O₃ [M+H]⁺ 233.1172, found 233.1182.

(E)-4-((3-(3-(trifluoromethyl)phenyl)allyl)oxy)but-2-yn-1-ol (1g)



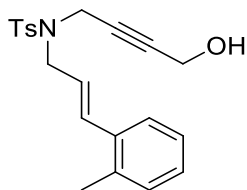
1g was isolated following the procedure **GP-4** using but-2-yne-1,4-diol (450 mg, 5.2 mmol) and (E)-3-(3-(trifluoromethyl)phenyl)allyl acetate (320 mg, 1.3 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1g** (41%, 145 mg, 0.54 mmol) as a pale yellow oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.61 (s, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 6.66 (d, J = 16.0 Hz, 1H), 6.34 (dt, J = 16.0, 5.9 Hz, 1H), 4.32 (s, 2H), 4.23 (d, J = 6.7 Hz, 4H), **¹³C NMR** (101 MHz, CDCl₃) δ = 137.4 (Cq), 131.6 (CH), 131.1 (q, J_{CF} = 32 Hz, Cq), 129.7 (CH), 129.1 (CH), 127.2 (CH), 124.4 (q, J_{CF} = 3.8 Hz, CH), 124.2 (q, J_{CF} = 272 Hz, Cq), 123.3 (q, $J_{C,F}$ = 4.0 Hz, CH), 85.1 (Cq), 81.5 (Cq), 70.0 (CH₂), 57.7 (CH₂), 51.0 (CH₂). **ESI-MS** calculated for C₁₄H₁₃F₃NaO₂ [M+Na]⁺ 293.08 found 293.16. **ESI- HRMS** calculated for C₁₄H₁₃F₃NaO₂ [M+Na]⁺ 293.0760 found 293.0769. **¹⁹F NMR** (565 MHz, CDCl₃) δ = -62.7 (s).

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



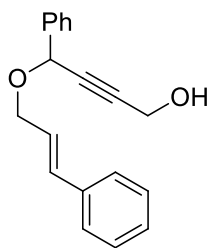
1h was isolated following procedure **GP-3** using *N*-cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (2.83 g, 8.7 mmol) and paraformaldehyde (784 mg, 26.1 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1h** (60%, 1860 mg, 5.2 mmol) as a white solid. Spectroscopic data correspond to the literature.³² ¹H NMR (300 MHz, CDCl₃) 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).

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



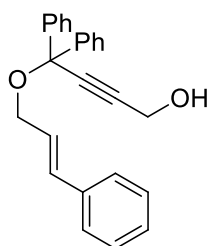
1i was isolated following procedure **GP-3** using (*E*)-4-methyl-*N*-(prop-2-yn-1-yl)-*N*-(3-(*o*-tolyl)allyl)benzenesulfonamide (399 mg, 1.2 mmol) and paraformaldehyde (106 mg, 3.5 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1i** (42%, 189 mg, 0.5 mmol) as a yellow solid. Spectroscopic data correspond to the literature.^[32] ¹H NMR (400 MHz, CDCl₃) δ = 7.78 (d, J = 8.3 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).

4-(cinnamyloxy)-4-phenylbut-2-yn-1-ol (**1j**)



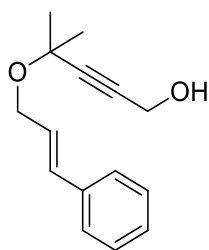
1j was isolated following procedure **GP-3** using (*E*)-(1-(cinnamyloxy)prop-2-yn-1-yl)benzene (500 mg, 2.0 mmol) and paraformaldehyde (181 mg, 6.0 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1j** (40%, 224 mg, 0.8 mmol) as a pale yellow oil. Spectroscopic data correspond to the literature.³² **¹H NMR** (400 MHz, CDCl₃) 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), 4.39-4.24 (m, 4H), 3.30 (brs, 1H).

4-(cinnamyloxy)-4,4-diphenylbut-2-yn-1-ol (**1k**)



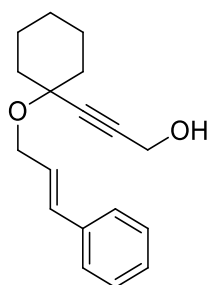
1k was isolated following procedure **GP-3** using **E1** (402.7 mg, 1.2 mmol) and paraformaldehyde (112 mg, 3.7 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1k** (86%, 368 mg, 1.04 mmol) as a white solid. **¹H NMR** (400 MHz, CDCl₃) δ = 7.69-7.62 (m, 4H), 7.46-7.28 (m, 11H), 6.71 (d, J = 16.0, 1.6 Hz, 1H), 6.41 (dt, J = 16.0, 5.7 Hz, 1H), 4.45 (s, 2H), 4.26 (dd, J = 5.7, 1.7 Hz, 2H), 2.12 (s, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.4 (2Cq), 137.0 (Cq), 131.6 (CH), 128.6 (2CH), 128.3 (4CH), 127.8 (2CH), 127.6 (CH), 126.8 (4CH), 126.5 (2CH), 126.4 (CH), 88.0 (Cq), 85.4 (Cq), 80.3 (Cq), 65.8 (CH₂), 51.3 (CH₂). **ESI-MS** calculated for C₂₅H₂₂NaO₂ [M+Na]⁺ 377.15, found 377.26. **ESI-HRMS** calculated for C₂₅H₂₂NaO₂ [M+Na]⁺ 377.1512, found 377.1506.

4-(cinnamyloxy)-4-methylpent-2-yn-1-ol (**1l**)



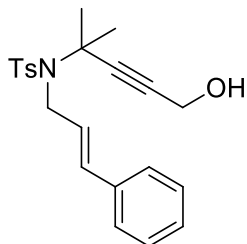
1l was isolated following procedure **GP-3** using (E)-(3-((2-methylbut-3-yn-2-yl)oxy)prop-1-en-1-yl)benzene (400 mg, 2.0 mmol) and paraformaldehyde (180 mg, 6.0 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1l** (34%, 155 mg, 0.67 mmol) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.39 (d, J = 7.1 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.25-7.20 (m, 1H), 6.62 (d, J = 15.9 Hz, 1H), 6.32 (dt, J = 15.9, 6.0 Hz, 1H), 4.31 (s, 2H), 4.27 (dd, J = 6.0, 1.5 Hz, 2H), 1.53 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 136.9 (Cq), 131.9 (CH), 128.6 (2CH), 127.6 (CH), 126.7 (CH), 126.5 (2CH), 87.8 (Cq), 82.6 (Cq), 70.5 (Cq), 65.2 (CH₂), 51.0 (CH₂), 28.9 (2CH₃). **ESI-MS** calculated for C₁₅H₁₈KO₂ [M+K]⁺ 269.09, found 269.21. **ESI-HRMS** calculated for C₁₅H₁₉O₂ [M+H]⁺ 231.1380, found 231.1387.

(E)-3-(1-(cinnamyloxy)cyclohexyl)prop-2-yn-1-ol (**1m**)



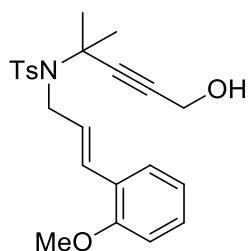
1m was isolated following procedure **GP-3** using **E2** (330 mg, 1.37 mmol) and paraformaldehyde (123 mg, 4.1 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1m** (41 %, 152 mg, 0.56 mmol) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.39 (dd, J = 8.2, 1.1 Hz, 2H), 7.30 (t, J = 7.6, 2H), 7.25-7.20 (m, 1H), 6.63 (d, J = 15.9 Hz, 1H), 6.33 (dt, J = 15.9, 5.9 Hz, 1H), 4.34 (s, 2H), 4.28 (dd, J = 6.0, 1.5 Hz, 2H), 1.98-1.90 (m, 3H), 1.74-1.63 (m, 4H), 1.60-1.48 (m, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 137.1 (Cq), 131.7 (CH), 128.6 (2CH), 127.6 (CH), 127.1 (CH), 126.6 (2CH), 87.1 (Cq), 84.3 (Cq), 73.9 (Cq), 64.3 (CH₂), 51.2 (CH₂), 37.3 (2CH₂), 25.5 (2CH₂), 22.9 (CH₂). **ESI-MS** calculated for C₁₈H₂₂NaO₂ [M+Na]⁺ 293.15, found 293.02. **ESI-HRMS** calculated for C₁₈H₂₁O₂ [M+H]⁺ 271.1692, found 271.1693.

N-cinnamyl-N-(5-hydroxy-2-methylpent-3-yn-2-yl)-4-methylbenzenesulfonamide (**1n**)



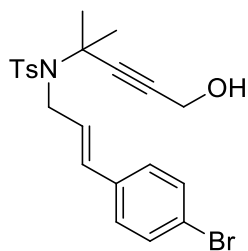
1n was isolated following procedure **GP-3** using N-cinnamyl-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (500 mg, 1.41 mmol) and paraformaldehyde (127 mg, 4.2 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1n** (75 %, 407 mg, 1.06 mmol) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.76 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 7.0 Hz, 2H), 7.32 (dd, *J* = 8.2, 6.7 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 3H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.36 (dt, *J* = 16.0, 6.2 Hz, 1H), 4.30 (dd, *J* = 6.2, 1.2 Hz, 2H), 4.12 (s, 2H), 2.40 (s, 3H), 1.69 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ = 143.1 (Cq), 139.9 (Cq), 136.8 (Cq), 132.4 (CH), 129.4 (2CH), 128.7 (2CH), 128.1 (CH), 127.8 (CH), 127.4 (2CH), 126.5 (2CH), 88.2 (Cq), 82.2 (Cq), 56.5 (Cq), 51.0 (CH₂), 50.1 (CH₂), 30.8 (2CH₃), 21.5 (CH₃). ESI-MS calculated for C₂₂H₂₅NNaO₃S [M+Na]⁺ 406.15, found 406.19. ESI-HRMS calculated for C₂₂H₂₄NO₃S [M+H]⁺ 384.1628, found 384.1621.

(E)-N-(5-hydroxy-2-methylpent-3-yn-2-yl)-N-(3-(2-methoxyphenyl)allyl)-4-methylbenzenesulfonamide (1o)



1o was isolated following procedure **GP-3** using **E3** (272 mg, 0.71 mmol) and paraformaldehyde (64 mg, 2.1 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1o** (33%, 98 mg, 0.24 mmol) as a yellow wax. ^1H NMR (400 MHz, CDCl_3) δ = 7.77 (d, J = 7.4 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.29 - 7.20 (m, 3H), 6.96 - 6.85 (m, 3H), 6.36 (dt, J = 16.1, 6.4 Hz, 1H), 4.32 (d, J = 6.4 Hz, 2H), 4.15 (s, 2H), 3.84 (s, 3H), 2.40 (s, 3H), 1.70 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ = 156.3 (Cq), 142.7 (Cq), 139.7 (Cq), 129.1 (2CH), 128.5 (CH), 128.3 (CH), 127.1 (2CH), 126.8 (CH), 126.5 (CH), 125.5 (Cq), 120.6 (CH), 110.7 (CH), 88.1 (Cq), 82.1 (Cq), 56.4 (Cq), 55.3 (CH_3), 50.7 (CH_2), 50.4 (CH_2), 30.5 (2 CH_3), 21.3 (CH_3). ESI-MS calculated for $\text{C}_{23}\text{H}_{27}\text{NNaO}_4\text{S}$ $[\text{M}+\text{Na}]^+$ 436.16, found 436.22. ESI-HRMS calculated for $\text{C}_{23}\text{H}_{26}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 414.1737, found 414.1743.

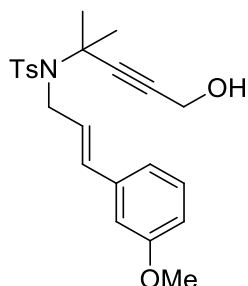
(E)-N-(3-(4-bromophenyl)allyl)-N-(5-hydroxy-2-methylpent-3-yn-2-yl)-4-methylbenzenesulfonamide (1p)



1p was isolated following procedure **GP-3** using **E4** (193 mg, 0.45 mmol) and paraformaldehyde (40 mg, 1.3 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1p** (56%, 115 mg, 0.25 mmol) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.75 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.28 - 7.22 (m, 4H), 6.51 (d, J = 15.9 Hz, 1H), 6.35 (dt, J = 15.9, 6.1 Hz, 1H), 4.28 (dd, J = 6.1, 1.4 Hz, 2H), 4.12 (d, J = 6.0 Hz, 2H), 2.40 (s, 3H), 1.68 (s,

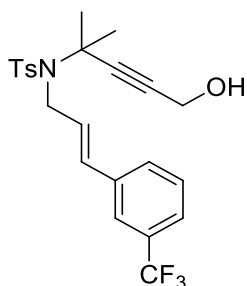
6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.2 (Cq), 139.8 (Cq), 135.8 (Cq), 131.8 (2CH), 131.2 (CH), 129.5 (2CH), 129.0 (CH), 128.1 (2CH), 127.5 (2CH), 121.6 (Cq), 88.3 (Cq), 82.1 (Cq), 56.5 (Cq), 51.1 (CH₂), 50.1 (CH₂), 30.8 (2CH₃), 21.6 (CH₃). **ESI-MS** calculated for C₂₂H₂₄⁸¹BrNNaO₃S [M+Na]⁺ 486.05, found 486.52. **ESI-HRMS** calculated for C₂₂H₂₄⁷⁹BrNNaO₃S [M+Na]⁺ 484.0552, found 484.0545.

E)-N-(5-hydroxy-2-methylpent-3-yn-2-yl)-N-(3-(3-methoxyphenyl)allyl)-4-methylbenzenesulfonamide (1q)



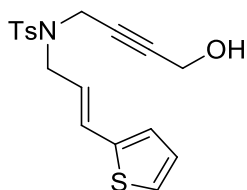
1o was isolated following procedure **GP-3** using **E5** (137 mg, 0.36 mmol) and paraformaldehyde (32 mg, 1.07 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1o** (70%, 105 mg, 0.25 mmol) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.80 (d, J = 8.3 Hz, 2H), 7.33-7.27 (m, 3H), 7.02 (d, J = 7.7 Hz, 1H), 6.98-6.95 (m, 1H), 6.85 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.58 (d, J = 16.0 Hz, 1H) 6.40 (dt, J = 16.0, 6.2 Hz, 1H), 4.34 (dd, J = 6.2, 1.4 Hz, 2H), 4.17 (s, 2H), 3.86 (s, 3H), 2.44 (s, 3H), 1.72 (s, 6H), 2.12 (s, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 159.8 (Cq), 143.1 (Cq), 139.6 (Cq), 138.2 (Cq), 132.2 (CH), 129.6 (CH), 129.4 (2CH), 128.3 (CH), 127.4 (2CH), 119.1(CH), 113.4 (CH), 111.7 (CH), 87.9 (Cq), 82.2 (Cq), 56.4 (Cq), 55.3 (CH₃), 50.8 (CH₂), 50.0 (CH₂), 30.7 (2CH₃), 21.5(CH₃). **ESI-MS** calculated for C₂₃H₂₇NNaO₄S [M+Na]⁺ 436.16, found 436.26. **ESI-HRMS** calculated for C₂₃H₂₇NNaO₄S [M+Na]⁺ 436.1553, found 436.1560.

(E)-N-(5-hydroxy-2-methylpent-3-yn-2-yl)-4-methyl-N-(3-(3-(trifluoromethyl)phenyl)allyl)benzenesulfonamide (1r)



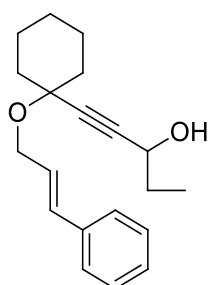
1r was isolated following procedure **GP-3** using **E6** (209 mg, 0.5mmol) and paraformaldehyde (45 mg, 1.5mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1r** (69%, 156 mg, 0.34 mmol) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.74(d, J = 8.3 Hz, 2H), 7.56 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 6.58 (d, J = 16.0 Hz, 1H), 6.40 (dt, J = 16.0, 6.0 Hz, 1H), 4.30 (dd, J = 6.1, 1.4 Hz, 2H), 4.11 (s, 2H), 2.37 (s, 3H), 1.67 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.3 (Cq), 139.4 (Cq), 137.5 (Cq), 130.9 (Cq, J_{CF} = 32.0 Hz), 130.8 (CH), 130.0 (CH), 129.6 (CH), 129.5 (2CH), 129.1 (CH), 127.4 (2CH), 124.1 (q, J_{CF} = 4.1 Hz, CH), 124.0 (q, J_{CF} = 272.3 Hz, Cq), 123.1 (q, J_{CF} = 4.1 Hz, CH), 87.8 (Cq), 82.3 (Cq), 56.5 (Cq), 50.8 (CH₂), 49.8 (CH₂), 30.7 (2CH₃), 21.4 (CH₃). **ESI-MS** calculated for C₂₃H₂₄F₃NNaO₃S [M+Na]⁺ 474.13, found 474.18. **ESI-HRMS** calculated for C₂₃H₂₄F₃NNaO₃S [M+Na]⁺ 474.1321, found 474.1318. **¹⁹F NMR** (565 MHz, CDCl₃) δ = -62.6 (s).

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



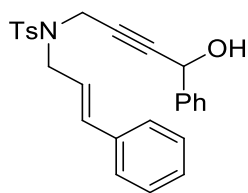
1s was isolated following procedure **GP-3** using (*E*)-4-methyl-*N*-(prop-2-yn-1-yl)-*N*-(3-(thiophen-2-yl)allyl)benzenesulfonamide (292 mg, 0.9 mmol) and paraformaldehyde (79 mg, 2.6 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1s** (37%, 118 mg, 0.3 mmol) as a yellow solid. Spectroscopic data correspond to the literature.³² **¹H NMR** (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.4 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 = 15.6, 6.8 Hz, 1H), 4.13 (t, J = 2.0 Hz, 2H), 4.00 (t, J = 1.9 Hz, 2H), 3.95 (d, J = 6.6 Hz, 2H), 2.44 (s, 3H).

(E)-1-(1-(cinnamyloxy)cyclohexyl)pent-1-yn-3-ol (**1t**)



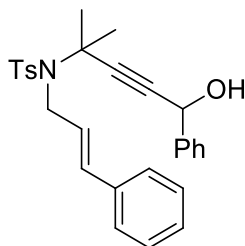
1t was isolated following procedure **GP-3** using (*E*)-(3-((1-ethynylcyclohexyl)oxy)prop-1-en-1-yl)benzene (300 mg, 1.25 mmol) and propionaldehyde (218 mg, 3.75 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1t** (36%, 135 mg, 0.45 mmol) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.38 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 6.62 (d, J = 15.9 Hz, 1H), 6.33 (dt, J = 15.9, 5.9 Hz, 1H), 4.41 (t, J = 6.4 Hz, 1H), 4.28 (d, J = 5.9 Hz, 2H), 2.00-1.90 (m, 2H), 1.80-1.60 (m, 8H), 1.55-1.50 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 137.1 (Cq), 131.7 (CH), 128.6 (2CH), 127.6 (CH), 127.1 (CH), 126.6 (2CH), 87.1 (Cq), 86.3 (Cq), 74.0 (Cq), 64.3 (CH₂), 63.9 (CH), 37.5 (CH₂), 37.4 (CH₂), 31.2 (CH₂), 25.6 (CH₂), 23.1 (2CH₂), 9.6 (CH₃). **ESI-MS** calculated for C₂₀H₂₆NaO₂ [M+Na]⁺ 321.18, found 321.24. **ESI-HRMS** calculated for C₂₀H₂₇O₂ [M+H]⁺ 299.2006, found 299.2014.

N-cinnamyl-N-(4-hydroxy-4-phenylbut-2-yn-1-yl)-4-methylbenzenesulfonamide (**1u**)



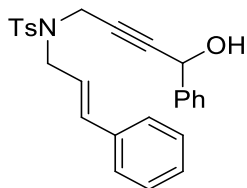
1u was isolated following procedure **GP-3** using (N-cinnamyl-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (186 mg, 0.57 mmol) and benzaldehyde (182 mg, 1.7 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1u** (47%, 117 mg, 0.27 mmol) as a brown solid. **¹H NMR** (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.3 Hz, 2H), 7.38-7.28 (m, 10H), 7.22 (d, J = 8.1 Hz, 2H), 6.50 (d, J = 15.9 Hz, 1H), 6.08 (dt, J = 15.8, 6.8 Hz, 1H), 5.21 (s, 1H), 4.22 (s, 2H), 3.98 (t, J = 6.0 Hz, 2H), 2.37 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.8 (Cq), 140.3 (Cq), 136.2 (2Cq), 135.0 (CH), 129.6 (2CH), 128.7 (2CH), 128.6 (2CH), 128.6 (CH), 128.2 (CH), 128.0 (2CH), 126.7 (2CH), 126.5 (2CH), 123.0 (CH), 85.7 (Cq), 79.7 (Cq), 64.3 (CH), 49.0 (CH₂), 36.4 (CH₂), 21.5 (CH₃). **ESI-MS** calculated for C₂₆H₂₅NNaO₃S [M+Na]⁺ 454.15, found 454.21. **ESI-HRMS** calculated for C₂₆H₂₆NO₃S [M+H]⁺ 432.1628, found 432.1622.

N-cinnamyl-N-(5-hydroxy-2-methyl-5-phenylpent-3-yn-2-yl)-4-methylbenzenesulfonamide (**1v**)



1v was isolated following procedure **GP-3** using N-cinnamyl-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (300 mg, 0.85 mmol) and benzaldehyde (180 mg, 1.7 mmol). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **1v** (70%, 274 mg, 0.60 mmol) as a yellow wax. **¹H NMR** (400 MHz, CDCl₃) δ = 7.74 (d, J = 8.1 Hz, 2H), 7.45-7.40 (m, 2H), 7.35-7.33 (m, 3H), 7.32-7.29 (m, 4H), 7.25-7.22 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 6.50 (d, J = 16.0 Hz, 1H), 6.34 (dt, J = 16.0, 6.2 Hz, 1H), 5.34 (d, J = 5.3 Hz, 1H), 4.31 (dd, J = 6.2, 1.3 Hz, 2H), 2.35 (s, 3H), 1.74 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.1 (Cq), 140.4 (Cq), 139.8 (Cq), 136.8 (Cq), 132.4 (CH), 129.5 (2CH), 128.7 (2CH), 128.7 (2CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.4 (2CH), 126.7 (2CH), 126.6 (2CH), 89.3 (Cq), 83.6 (Cq), 64.6 (CH), 56.7 (Cq), 50.3 (CH₂), 30.9 (2CH₃), 21.6 (CH₃). **ESI-MS** calculated for C₂₈H₃₀NO₃S [M+H]⁺ 460.19, found 460.30. **ESI-HRMS** calculated for C₂₈H₃₀NO₃S [M+H]⁺ 460.1941, found 460.1950.

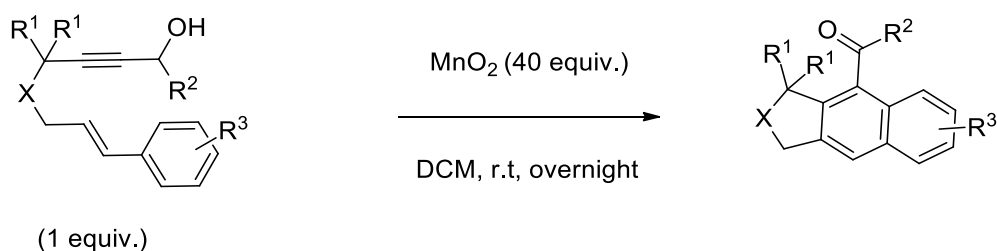
***N*-cinnamyl-4-methyl-*N*-(4-oxo-4-phenylbut-2-yn-1-yl)benzenesulfonamide (**3u**)**



3u was prepared following procedure **GP-3** using *N*-cinnamyl-*N*-propargylbenzenesulfonamide (650 mg, 2.0 mmol, 1 equiv.) and benzoyl chloride (309 mg, 2.2 mmol, 1.1 equiv.). Purification by column chromatography (eluent: gradient hexane to hexane/EtOAc 7:3) afforded **3u** (37%, 318 mg, 0.74 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.88-7.84 (m, 2H), 7.82- 7.77 (m, 2H), 7.64-7.59 (m, 1H), 7.45-7.40 (m, 2H), 7.36-7.20 (m, 7H), 6.62 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.8, 6.86 Hz, 1H), 4.42 (s, 2H), 4.09 (d, *J* = 6.85, 0.90 Hz, 2H), 2.23 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 176.8 (C=O), 144.3 (2Cq), 136.1 (Cq), 135.9 (Cq), 134.4 (CH), 129.9 (2CH), 129.5 (2CH), 128.7 (2CH), 128.7 (2CH), 128.3 (CH), 127.8 (2CH), 126.7 (2CH), 122.5 (CH), 87.1 (Cq), 83.5 (Cq), 49.5 (CH₂), 36.4 (CH₂), 21.5 (CH₃). ESI-HRMS calculated for C₂₆H₂₆NO₃S [M+H]⁺ 432.1628, found 432.1635.

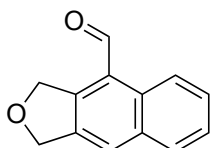
Characterization of products

Catalytic synthesis of products (GP-5)



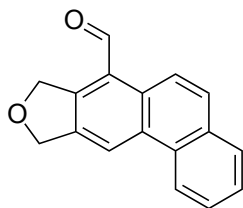
The styryl-ynol (0.25 mmol, 1 equiv.) was dissolved in DCM (30 ml, 0.0083 M) and then MnO_2 (870 mg, 1 mmol, 40 equiv.) was added. The mixture was stirred overnight at room temperature. The solid was removed by filtration over a pad of celite and the crude was concentrated under reduced pressure. Purification by column chromatography (hexane:EtOAc = 8:2) afforded the desired product.

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



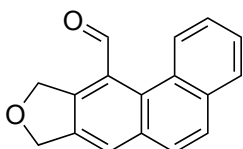
Product **2a** was isolated following **GP-5** as a white solid (63%, 31.4 mg, 0.16 mmol) using **1a** (50.6 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **^1H NMR** (400 MHz, CDCl_3) δ = 10.94 (s, 1H, CHO), 8.76 (dd, J = 8.6 Hz, 3.1 Hz, 1H), 7.92-7.90 (m, 2H), 7.68-7.64 (m, 1H), 7.59-7.55 (m, 1H), 5.53 (s, 2H), 5.22 (s, 2H). **^{13}C NMR** (101 MHz, CDCl_3) δ = 190.3 (C=O), 144.3 (Cq), 138.7 (Cq), 133.8 (Cq), 131.9 (Cq), 129.1 (CH), 128.3 (CH), 126.5 (CH), 126.3 (CH), 123.9 (Cq), 122.5 (CH), 74.1 (CH_2), 71.7 (CH_2). **ESI-MS** calculated for $\text{C}_{13}\text{H}_{10}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 221.05, found 221.02. **ESI-HRMS** calculated for $\text{C}_{13}\text{H}_{10}\text{KO}_2$ $[\text{M}+\text{K}]^+$ 237.0312, found 237.0309.

8,10-dihydrophenanthro[2,3-c]furan-7-carbaldehyde (2b)



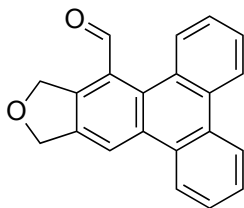
Product **2b** was isolated following **GP-5** as a white solid (50%, 32 mg, 0.13 mmol) using **1b** (63 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.97 (s, 1H, CHO), 8.72 (s, 1H), 8.63-8.55 (m, 2H), 7.93 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.75-7.62 (m, 2H), 5.54 (s, 2H), 5.28 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ = 190.6 (C=O), 143.0 (Cq), 139.2 (Cq), 131.5 (Cq), 131.4 (Cq), 130.9 (Cq), 130.1 (Cq), 129.5 (CH), 128.8 (CH), 127.5 (CH), 127.4 (CH), 124.9 (Cq), 122.7 (CH), 120.7 (CH), 120.2 (CH), 74.7 (CH₂), 72.5 (CH₂). **ESI-MS** calculated for C₁₇H₁₂NaO₂ [M+Na]⁺ 271.07, found 271.01. **ESI-HRMS** calculated for C₁₇H₁₃O₂ [M+H]⁺ 249.0910, found 249.0919.

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



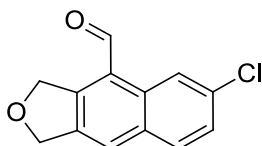
Product **2c** was isolated following **GP-5** as a white solid (59%, 36 mg, 0.15 mmol) using **1c** (63 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.58 (s, 1H, CHO), 8.05 (d, J = 7.2 Hz, 1H), 7.98 (d, J = 7.2 Hz, 1H), 7.90 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.73-7.64 (m, 2H), 5.50 (s, 2H), 5.29 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ = 192.5 (C=O), 142.0 (Cq), 139.2 (Cq), 133.6 (Cq), 133.3 (Cq), 130.6 (Cq), 129.3 (CH), 128.7 (CH), 128.6 (Cq), 128.1 (Cq), 128.0 (CH), 127.7 (CH), 126.9 (CH), 126.7 (CH), 124.9 (CH), 74.9 (CH₂), 72.6 (CH₂). **ESI-MS** calcd for C₁₇H₁₂NaO₂ [M+Na]⁺ 271.21, found 271.05. **ESI-HRMS** calculated for C₁₇H₁₃O₂ [M+H]⁺ 249.0910, found 249.0909.

10,12-dihydrotriphenyleno[2,3-c]furan-9-carbaldehyde (2d)



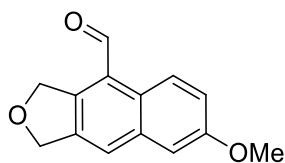
Product **2d** was isolated following **GP-5** as a white solid (67%, 53.7 mg, 0.18 mmol) using **1d** (81.4 mg, 0.27 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.34 (s, 1H, CHO), 8.70-7.60 (m, 3H), 8.57-8.53 (m, 1H), 7.85 (d, J = 8.0, 1.3 Hz, 1H), 7.80-7.62 (m, 4H), 5.52 (s, 2H), 5.33 (d, J = 1.4 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ = 192.3 (C=O), 141.8 (Cq), 139.7 (Cq), 131.6 (Cq), 131.3 (2Cq), 131.0 (CH), 130.0 (Cq), 129.3 (Cq), 128.6 (CH), 128.5 (Cq), 128.1 (CH), 128.0 (CH), 127.7 (Cq), 126.9 (CH), 123.9 (CH), 123.5 (CH), 123.3 (CH), 119.4 (CH), 75.1 (CH₂), 73.0 (CH₂). **ESI-MS** calculated for C₂₁H₁₅O₂ [M+H]⁺ 299.11, found 299.18. **ESI-HRMS** calculated for C₂₁H₁₅O₂ [M+H]⁺ 299.1067, found 299.1072.

6-chloro-1,3-dihydronaphtho[2,3-c]furan-4-carbaldehyde (2e)



Product **2e** was isolated following **GP-5** as a white solid (54%, 31.7 mg, 0.16 mmol) using **1e** (59.2 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.77 (s, 1H, CHO), 8.80 (s, 1H), 7.88 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.52 (dd, J = 8.8, 2.0 Hz, 1H), 5.53 (s, 2H), 5.20 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ = 189.6 (C=O), 145.8 (Cq), 139.1 (Cq), 134.7 (Cq), 132.2 (Cq), 132.0 (Cq), 130.3 (CH), 127.6 (CH), 126.1 (CH), 123.1 (Cq), 122.2 (CH), 73.8 (CH₂), 71.8 (CH₂). **ESI-MS** calculated for C₁₃H₁₀ClO₂ [M+H]⁺ 233.04, found 233.20. **ESI-HRMS** calculated for C₁₃H₁₀ClO₂ [M+H]⁺ 233.0364, found 233.0356.

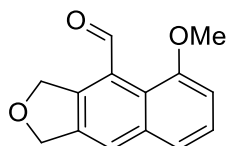
7-methoxy-1,3-dihydronaphtho[2,3-c]furan-4-carbaldehyde (**2f**)



2f

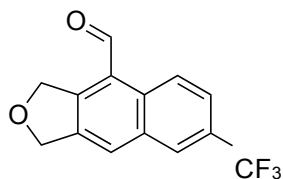
Product **2f** was isolated following **GP-5** as a yellow solid (28%, 34.4 mg, 0.15 mmol) using **1f** (125 mg, 0.54 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.82 (s, 1H, CHO), 8.65 (d, J = 9.3 Hz, 1H), 7.77 (s, 1H), 7.29 (dd, J = 9.3, 2.7 Hz, 1H), 7.16 (d, J = 2.6 Hz, 1H), 5.48 (s, 2H), 5.17 (s, 2H), 3.93 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 190.4 (C=O), 157.8 (Cq), 141.8 (Cq), 139.2 (Cq), 135.4 (Cq), 127.1 (Cq), 125.0 (CH), 124.0 (CH), 123.9 (Cq), 120.8 (CH), 107.0 (CH), 74.0 (CH₂), 71.9 (CH₂), 55.4 (CH₃). **ESI-MS** calculated for C₁₄H₁₂KO₃ [M+K]⁺ 267.04, found 267.11. **ESI-HRMS** calculated for C₁₄H₁₂NaO₃ [M+Na]⁺ 251.0679, found 251.0684.

5-methoxy-1,3-dihydronaphtho[2,3-c]furan-4-carbaldehyde (**2f'**)



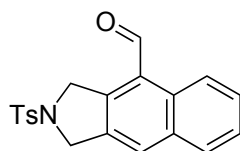
Product **2f'** was isolated following **GP-5** as a yellow solid (11%, 13.8 mg, 0.06 mmol) using **1f** (125 mg, 0.54 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 11.13 (s, 1H, CHO), 7.81 (s, 1H), 7.51-7.41 (m, 2H), 7.00 (dd, J = 7.4, 1.2 Hz, 1H), 5.40 (s, 2H), 5.19 (s, 2H), 4.03 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 195.6 (C=O), 156.7 (Cq), 142.2 (Cq), 139.1 (Cq), 135.7 (Cq), 127.3 (Cq), 126.6 (CH), 124.6 (CH), 123.2 (Cq), 121.7 (CH), 107.1 (CH), 74.9 (CH₂), 72.0 (CH₂), 55.9 (CH₃). **ESI-MS** calculated for C₁₄H₁₃O₃ [M+H]⁺ 229.09, found 229.52. **ESI-HRMS** calculated for C₁₄H₁₂NaO₃ [M+Na]⁺ 251.0679, found 251.0671.

7-(trifluoromethyl)-1,3-dihydronaphtho[2,3-c]furan-4-carbaldehyde (2g)



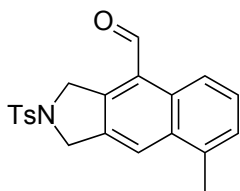
Product **2g** was isolated following **GP-5** as a white solid (17%, 24 mg, 0.09 mmol) using **1g** (140 mg, 0.52 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.92 (s, 1H, CHO), 8.94 (d, J = 8.9 Hz, 1H), 8.20 (s, 1H), 8.02 (s, 1H), 7.83 (dd, J = 8.9, 1.9 Hz, 1H), 5.57 (s, 2H), 5.26 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ = 189.6 (C=O), 146.8 (Cq), 140.3 (2Cq), 132.9 (Cq), 132.7 (Cq), 128.4 (q, J_{CF} = 33.4 Hz, Cq), 126.8 (CH), 126.4 (q, J_{CF} = 4.2 Hz, CH), 124.0 (q, J_{CF} = 27.2 Hz, Cq), 123.9 (CH), 123.9 (q, J_{CF} = 2.4 Hz, CH), 73.8 (CH₂), 71.7 (CH₂). **ESI-MS** calculated for C₁₄H₉F₃NaO₂ [M+Na]⁺ 305.02, found 305.42. **ESI-HRMS** calculated for C₁₄H₉F₃NaO₂ [M+Na]⁺ 289.0447, found 289.0451. **¹⁹F NMR** (565 MHz, CDCl₃) δ = -62.5 (s).

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



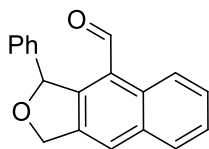
Product **2h** was isolated following **GP-5** as a white solid (48%, 42 mg, 0.12 mmol) using **1h** (88 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.94 (s, 1H, CHO), 8.71 (d, J = 8.6 Hz, 1H), 7.90-7.80 (m, 4H), 7.68-7.61 (m, 1H), 7.61-7.52 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 5.06 (s, 2H), 4.75 (s, 2H), 2.38 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 190.0 (C=O), 143.9 (Cq), 140.2 (Cq), 135.4 (Cq), 133.6 (Cq), 133.4 (Cq), 131.7 (Cq), 129.9 (2CH), 128.9 (CH), 128.5 (CH), 127.9 (CH), 127.7 (2CH), 126.7 (CH), 124.5 (Cq), 122.2 (CH), 54.3 (CH₂), 52.1 (CH₂), 21.5 (CH₃). **ESI-MS** calculated for C₂₀H₁₇NNaO₃S [M+Na]⁺ 374.08, found 374.07. **ESI-HRMS** calculated for C₂₀H₁₇NNaO₃S [M+Na]⁺ 374.0821, found 374.0816.

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



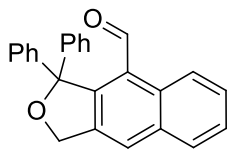
Product **2i** was isolated following **GP-5** as a white solid (23%, 22 mg, 0.06 mmol) using **1i** (92 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.96 (s, 1H, CHO), 8.56 (d, J = 8.7 Hz, 1H), 8.07 (s, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.56-7.49 (m, 1H), 7.39 (d, J = 6.9 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H), 5.07 (s, 2H), 4.79 (s, 2H), 2.69 (s, 3H), 2.38 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 190.6 (C=O), 144.0 (Cq), 139.5 (Cq), 135.3 (Cq), 135.2 (Cq), 133.6 (Cq), 133.1 (Cq), 132.3 (Cq), 130.0 (2CH), 128.2 (CH), 127.8 (2CH), 127.6 (CH), 125.1 (Cq), 124.2 (CH), 120.4 (CH), 54.7 (CH₂), 52.5 (CH₂), 21.6 (CH₃), 20.1 (CH₃). **ESI-MS** calculated for C₂₁H₁₉NNaO₃S [M+Na]⁺ 388.10, found 388.07. **ESI-HRMS** calculated for C₂₁H₁₉NNaO₃S [M+Na]⁺ 388.0978, found 388.0987.

3-phenyl-1,3-dihydronaphtho[2,3-c]furan-4-carbaldehyde (2j)



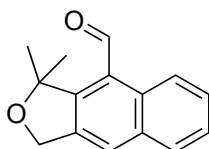
Product **2j** was isolated following **GP-5** as a white solid (31%, 21 mg, 0.08 mmol) using **1j** (69 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.55 (s, 1H, CHO), 9.01 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.70-7.57 (m, 2H), 7.34-7.27 (m, 3H), 7.22-7.16 (m, 2H), 6.82 (s, 1H), 5.36 (d, J = 12.8 Hz, 1H), 5.27 (d, J = 12.8 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 190.6 (C=O), 146.9 (Cq), 141.5 (Cq), 139.2 (Cq), 134.3 (Cq), 131.3 (Cq), 128.9 (2CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 127.9 (2CH), 127.0 (CH), 126.5 (CH), 124.7 (CH), 124.6 (Cq), 85.7 (CH), 71.1 (CH₂). **ESI-MS** calcd for C₁₉H₁₄NaO₂ [M+Na]⁺ 297.09, found 297.03. **ESI-HRMS** calcd for C₁₉H₁₄NaO₂ [M+Na]⁺ 297.0886, found 297.0894.

3,3-diphenyl-1,3-dihydronaphtho[2,3-c]furan-4-carbaldehyde (2k)



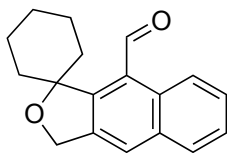
Product **2k** was isolated following **GP-5** as a white solid (80%, 70.7 mg, 0.20 mmol) using **1k** (89.2 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.21 (s, 1H, CHO), 9.21 (d, J = 7.5 Hz, 1H), 7.96 (s, 1H), 7.90 (d, J = 7.4 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.39-7.33 (m, 10H), 5.16 (d, J = 1.3 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ = 193.1 (C=O), 150.4 (Cq), 142.6 (2Cq), 139.4 (Cq), 134.2 (Cq), 130.3 (Cq), 129.0 (CH), 128.8 (4CH), 128.5 (4CH), 128.4 (2CH), 128.37 (CH), 127.1 (CH), 126.6 (CH), 126.3 (CH), 125.7 (Cq), 93.5 (Cq), 69.7 (CH₂). **ESI-MS** calculated for C₂₅H₁₈NaO₂ [M+Na]⁺ 373.12, found 373.17. **ESI HRMS** calculated for C₂₅H₁₈NaO₂ [M+Na]⁺ 373.1199, found 373.1206.

3,3-dimethyl-1,3-dihydronaphtho[2,3-c]furan-4-carbaldehyde (2l)



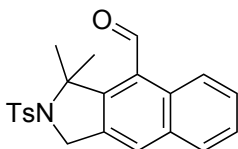
Product **2l** was isolated following **GP-5** as a white solid (71%, 41.1 mg, 0.18 mmol) using **1l** (58.9 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.92 (s, 1H, CHO), 9.04 (d, J = 7.5 Hz, 1H), 7.87-7.82 (m, 2H), 7.62 (t, J = 7.7 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 5.19 (s, 2H), 1.80 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 191.5 (C=O), 151.9 (Cq), 138.7, (Cq), 133.8 (Cq), 131.0 (Cq), 128.6 (CH), 128.4 (CH), 126.8 (CH), 126.3 (CH), 125.5 (CH), 124.7 (Cq), 86.7 (Cq), 69.3 (CH₂), 29.3 (2CH₃). **ESI-MS** calculated for C₁₅H₁₅O₂ [M+H]⁺ 227.11, found 227.44. **ESI-HRMS** calculated for C₁₅H₁₄O₂Na [M+Na]⁺ 249.0886, found 249.0881.

3'H-spiro[cyclohexane-1,1'-naphtho[2,3-c]furan]-9'-carbaldehyde (2m)



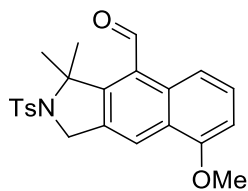
Product **2m** was isolated following **GP-5** as a white solid (75%, 49.7 mg, 0.19 mmol) using **1m** (67.9 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 11.00 (s, 1H, CHO), 9.02 (d, J = 8.13 Hz, 1H), 7.85-7.81 (m, 2H), 7.60 (t, J = 7.7 Hz, 1H), 7.52 (ddd, J = 8.1 Hz, 6.8, 1.2 Hz, 1H), 5.18 (s, 2H), 2.10-2.00 (m, 4H), 1.86-1.70 (m, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 192.0 (C=O), 151.5 (Cq), 138.7 (Cq), 133.6 (Cq), 130.8 (Cq), 128.5 (CH), 128.3 (CH), 126.7 (CH), 126.1 (CH), 125.8 (CH), 125.4 (Cq), 88.1 (Cq), 69.2 (CH₂), 37.4 (2CH₂), 25.3 (CH₂), 22.8 (2CH₂). **ESI-MS** calculated for C₁₈H₁₈KO₂ [M+K]⁺ 305.09, found 305.15. **ESI-HRMS** calculated for C₁₈H₁₈NaO₂ [M+Na]⁺ 289.1199, found 289.1192.

3,3-dimethyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-4-carbaldehyde (2n)



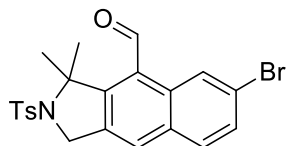
Product **2n** was isolated following **GP-5** as an orange solid (90%, 88.8 mg, 0.23 mmol) using **1n** (100 mg, 0.26 mmol) as reagent (eluent: hexane:EtOAc = 8:2). Product **2n** was isolated following **GP-5** as an orange solid (67%, 254 mg, 0.67 mmol) using **1n** (384 mg, 1.0 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 11.00 (s, 1H, CHO), 8.74 (d, J = 8.7 Hz, 1H), 7.85-7.77 (m, 4H), 7.60-7.55 (m, 2H), 7.29 (d, J = 8.1 Hz, 2H), 4.75 (s, 2H), 2.4 (s, 3H), 2.09 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 192.3 (C=O), 149.2 (Cq), 143.5 (Cq), 137.9 (Cq), 133.3 (Cq), 132.7 (Cq), 131.1 (Cq), 129.7 (2CH), 128.5 (CH), 128.2 (CH), 127.5 (2CH), 127.1 (CH), 126.9 (CH), 126.3 (Cq), 125.3 (CH), 72.4 (Cq), 51.9 (CH₂), 29.7 (2CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₂H₂₁KNO₃S [M+K]⁺ 418.09, found 418.01. **ESI-HRMS** calculated for C₂₂H₂₁NaNO₃S [M+Na]⁺ 402.1134, found 402.1137.

8-methoxy-3,3-dimethyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-4-carbaldehyde (**2o**)



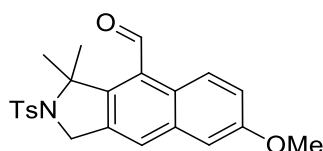
Product **2o** was isolated following **GP-5** as a yellow solid (70%, 40.3 mg, 0.10 mmol) using **1o** (57.8 mg, 0.14 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 11.01 (s, 1H, CHO), 8.31 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.49 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 7.6 Hz, 1H), 4.76 (d, J = 1.3 Hz, 2H), 3.98 (s, 3H), 2.40 (s, 3H), 2.09 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 192.6 (C=O), 155.3 (Cq), 149.3 (Cq), 143.5 (Cq), 138.0 (Cq), 132.4 (Cq), 131.9 (Cq), 129.7 (2CH), 128.8 (CH), 127.5 (2CH), 126.0 (Cq), 125.8 (Cq), 121.6 (CH), 117.2 (CH), 104.7 (CH), 72.6 (Cq), 55.8 (CH₃), 52.2 (CH₂), 29.6 (2CH₃), 21.6 (CH₃). **ESI-MS** calculated for C₂₃H₂₃NNaO₄S [M+Na]⁺ 432.12, found 432.32. **ESI-HRMS** calculated for C₂₃H₂₄NO₄S [M+H]⁺ 410.1421, found 410.1430.

6-bromo-3,3-dimethyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-4-carbaldehyde (**2p**)



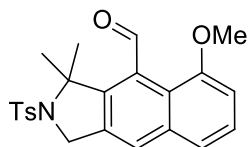
Product **2p** was isolated following **GP-5** as a white solid (64%, 64.5 mg, 0.14 mmol) using **1p** (102.6 mg, 0.22 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.95 (s, 1H, CHO), 9.07 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.78 (s, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.61 (dd, J = 8.7, 1.9 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 4.73 (d, J = 1.3 Hz, 2H), 2.42 (s, 3H), 2.12 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 191.5 (C=O), 150.9 (Cq), 143.7 (Cq), 137.8 (Cq), 133.3 (Cq), 131.9 (Cq), 131.8 (Cq), 130.7 (CH), 129.8 (2CH), 129.5 (CH), 128.2 (CH), 127.6 (2CH), 127.3 (CH), 125.3 (Cq), 123.7 (Cq), 72.4 (Cq), 51.9 (CH₂), 30.2 (2CH₃), 21.7 (CH₃). **ESI-MS** calculated for C₂₂H₂₀⁸¹BrNNaO₃S [M+Na]⁺ 482.02, found 482.23. **ESI-HRMS** calculated for C₂₂H₂₁⁷⁹BrNO₃S [M+H]⁺ + 458.0420, found 458.0423

6-methoxy-3,3-dimethyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-4-carbaldehyde (**2q**)



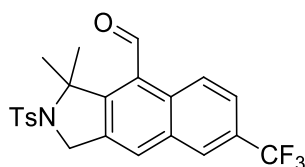
Product **2q** was isolated in mixture with **2q'** following **GP-5** as a yellow solid (90% combined yield, 1:0.58 **2q/2q'** ratio, 75.2 mg, 0.18 mmol) using **1q** (84.7 mg, 0.20 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.97 (s, 1H, CHO), 8.72 (d, J = 9.4 Hz, 1H), 7.85 (d, J = 7.8 Hz, 2H), 7.72 (s, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.26 (dd, J = 9.5, 2.7 Hz, 1H), 7.09 (d, J = 2.7 Hz, 1H), 4.76 (s, 2H), 3.93 (s, 3H), 2.43 (s, 3H), 2.11 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 192.3 (C=O), 158.1 (Cq), 147.2 (Cq), 143.5 (Cq), 137.8 (Cq), 135.0 (Cq), 133.2 (Cq), 129.7 (2CH), 127.5 (2CH), 127.0 (CH), 126.4 (Cq), 126.2 (Cq), 126.0 (CH), 121.2 (CH), 106.0 (CH), 72.4 (CH₃), 55.4 (Cq), 52.0 (CH₂), 30.1 (2CH₃), 21.6 (CH₃). **ESI-MS** calculated for C₂₃H₂₃NNaO₄S [M+Na]⁺ 432.12, found 432.35. **ESI-HRMS** calculated for C₂₃H₂₄NO₄S [M+H]⁺ 410.1421, found 410.1415

5-methoxy-3,3-dimethyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-4-carbaldehyde (2q')



Product **2q'** was isolated in mixture with **2q** following **GP-5** as a yellow solid (90% combined yield, 1:0.58 **2q/2q'** ratio, 75.2 mg, 0.18 mmol) using **1q** (84.7 mg, 0.20 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.84 (s, 1H, CHO), 7.81 (d, J = 8.3 Hz, 2H), 7.63 (s, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.39 (s, 1H), 7.28 (d, J = 7.1 Hz, 2H), 6.84 (m, 1H), 4.72 (s, 2H), 3.93 (s, 3H), 2.40 (s, 3H), 1.90 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 196.5 (C=O), 155.6 (Cq), 143.3 (Cq), 142.5 (Cq), 137.9 (Cq), 134.4 (Cq), 133.7 (Cq), 130.5 (CH), 129.6 (2CH), 127.5 (2CH), 127.1 (Cq), 123.0 (Cq), 122.7 (CH), 120.9 (CH), 106.1 (CH), 72.2 (CH₃), 56.1 (Cq), 52.0 (CH₂), 28.5 (2CH₃), 21.6 (CH₃). **ESI-MS** calculated for C₂₃H₂₃NNaO₄S [M+Na]⁺ 432.12, found 432.35. **ESI-HRMS** calculated for C₂₃H₂₄NO₄S [M+H]⁺ 410.1421, found 410.1415.

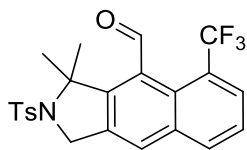
3,3-dimethyl-2-tosyl-7-(trifluoromethyl)-2,3-dihydro-1H-benzo[f]isoindole-4-carbaldehyde (2r)



Product **2r** was isolated following **GP-5** as a brown solid (52%, 57.9 mg, 0.13 mmol) using **1r** (113 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 11.00 (s, 1H, CHO), 8.89 (d, J = 9.1 Hz, 1H), 8.08 (s, 1H), 7.89 (s, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 4.77 (s, 2H), 2.41 (s, 3H), 2.12 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 191.7 (C=O), 151.6 (Cq), 143.8 (Cq), 137.6 (Cq), 134.4 (Cq), 132.3 (Cq), 132.2 (Cq), 129.8 (2CH), 128.8 (q, J_{CF} = 32.7 Hz, Cq), 127.8 (CH), 127.5 (2CH), 126.9 (CH), 126.4 (Cq), 125.6 (q, J_{CF} = 4.36 Hz, CH), 123.99 (q, J_{CF} = 2.7 Hz, CH), 123.97 (q, J_{CF} = 272 Hz, Cq), 72.3 (Cq), 51.8 (CH₂), 29.9 (2CH₃), 21.6 (CH₃). **ESI-MS** calculated for C₂₃H₂₀F₃NNaO₃S [M+Na]⁺ 470.10, found 470.22. **ESI-HRMS** calculated for C₂₃H₂₁F₃NO₃S [M+H]⁺ 448.1188, found 448.1195. **¹⁹F NMR** (565 MHz,

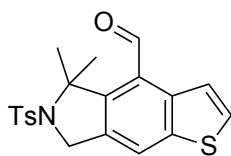
CDCl_3) $\delta = -62.6$ (s).

3,3-dimethyl-2-tosyl-5-(trifluoromethyl)-2,3-dihydro-1H-benzo[f]isoindole-4-carbaldehyde (2r')



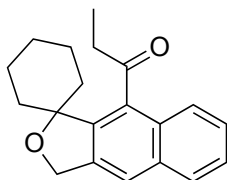
Product **2r'** was isolated following **GP-5** as a brown solid (28%, 33.3 mg, 0.07 mmol) using **1r** (113 mg, 0.25 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.78 (q, J = 2.86 Hz, CHO), 8.0 (d, J = 7.79 Hz, 2H), 7.81 (m, 3H), 7.59 (t, J = 7.9 Hz, 1H), 7.30 (d, J = 7.6 Hz, 2H), 4.75 (d, J = 1.3 Hz, 2H), 2.41 (s, 3H), 2.00 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 194.1 (q, J_{CF} = 5.4 Hz, C=O), 147.1 (Cq), 143.6 (Cq), 137.9 (Cq), 134.3 (Cq), 133.9 (Cq), 133.6 (CH), 130.2 (Cq), 129.8 (2CH), 129.0 (q, J_{CF} = 6.6 Hz, CH), 127.5 (2CH), 126.0 (q, J_{CF} = 31 Hz, Cq), 125.6 (CH), 125.5 (CH), 124.5 (q, J = 273 Hz, Cq), 72.9 (Cq), 51.7 (CH₂), 28.5 (2CH₃), 21.6 (CH₃). **ESI-MS** calculated for C₂₃H₂₀F₃NNaO₃S [M+Na]⁺ 470.10, found 470.45. **ESI-HRMS** calculated for C₂₃H₂₁F₃NO₃S [M+H]⁺ 448.1188, found 448.1184. **¹⁹F NMR** (565 MHz, CDCl₃) δ = -54.6 (s).

5-tosyl-6,7-dihydro-5H-thieno[2,3-f]isoindole-4-carbaldehyde (2s)



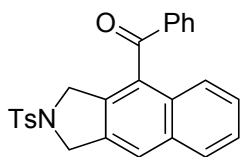
Product **2s** was isolated following **GP-5** as a white solid (41%, 13 mg, 0.04 mmol) using **1s** (32.1 mg, 0.09 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 10.58 (s, 1H, CHO), 8.04 (d, J = 5.7 Hz, 1H), 7.90 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 5.04 (s, 2H), 4.72 (s, 2H), 2.39 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 189.6 (C=O), 144.0 (Cq), 141.7 (Cq), 139.4 (Cq), 136.8 (Cq), 134.3 (Cq), 133.7 (Cq), 131.0 (CH), 130.1 (2CH), 127.8 (2CH), 124.3 (Cq), 122.3 (CH), 120.6 (CH), 53.7 (CH₂), 52.4 (CH₂), 21.6 (CH₃). **ESI-MS** calculated for C₁₈H₁₆NO₃S₂ [M+H]⁺ 358.06, found 358.14. **ESI-HRMS** calculated for C₁₈H₁₆NO₃S₂ [M+H]⁺ 358.0879, found 358.0887.

1-(3'H-spiro[cyclohexane-1,1'-naphtho[2,3-c]furan]-9'-yl)propan-1-one (2t)



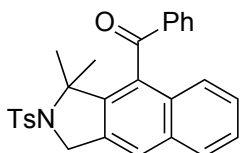
Product **2t** was isolated following **GP-5** as a white solid (9%, 6.5 mg, 0.02 mmol) using **1t** (72 mg, 0.24 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.84-7.80 (m, 1H), 7.66 (s, 1H), 7.56-7.53 (m, 1H), 7.49-7.45 (m, 2H), 5.11 (s, 2H), 2.99 (q, J = 7.2 Hz, 2H), 1.87-1.64 (m, 10H), 1.31 (t, J = 7.2 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 210.1 (C=O), 140.8 (Cq), 139.1 (Cq), 133.3 (Cq), 133.1 (Cq), 129.4 (Cq), 128.4 (CH), 126.4 (CH), 126.2 (CH), 124.5 (CH), 120.6 (CH), 87.0 (Cq), 69.0 (CH₂), 40.0 (CH₂), 35.2 (CH₂), 25.2 (CH₂), 22.6 (3CH₂), 7.7 (CH₃). **ESI-MS** calculated for C₂₀H₂₂NaO₂ [M+Na]⁺ 317.15, found 317.52. **ESI-HRMS** calculated for C₂₀H₂₂NaO₂ [M+Na]⁺ 317.1512, found 317.1518.

Phenyl(2-tosyl-2,3-dihydro-1H-benzo[f]isoindol-4-yl)methanone (**2u**)



Product **2u** was isolated following **GP-5** as a white solid (8%, 16 mg, 0.04 mmol) using **1u** (211.8 mg, 0.5 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.83 (d, J = 8.2 Hz, 1H), 7.77-7.70 (m, 5H), 7.63 (t, J = 7.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.48-7.42 (m, 3H), 7.36 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 4.77 (s, 2H), 4.51 (s, 2H), 2.39 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 197.4 (C=O), 143.9 (Cq), 136.8 (Cq), 134.7 (Cq), 134.3 (CH), 133.4 (Cq), 133.2 (2Cq), 131.7 (Cq), 130.3 (Cq), 129.9 (4CH), 129.0 (2CH), 128.2 (CH), 127.7 (2CH), 126.9 (CH), 126.5 (CH), 125.4 (CH), 123.1 (CH), 53.0 (CH₂), 52.4 (CH₂), 21.5 (CH₃). **ESI-MS** calculated for C₂₆H₂₁NNaO₃S [M+Na]⁺ 450.11, found 450.45. **ESI-HRMS** calculated for C₂₆H₂₂NO₃S [M+H]⁺ 428.1315, found 428.1306.

(3,3-dimethyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindol-4-yl)(phenyl)methanone (**2v**)



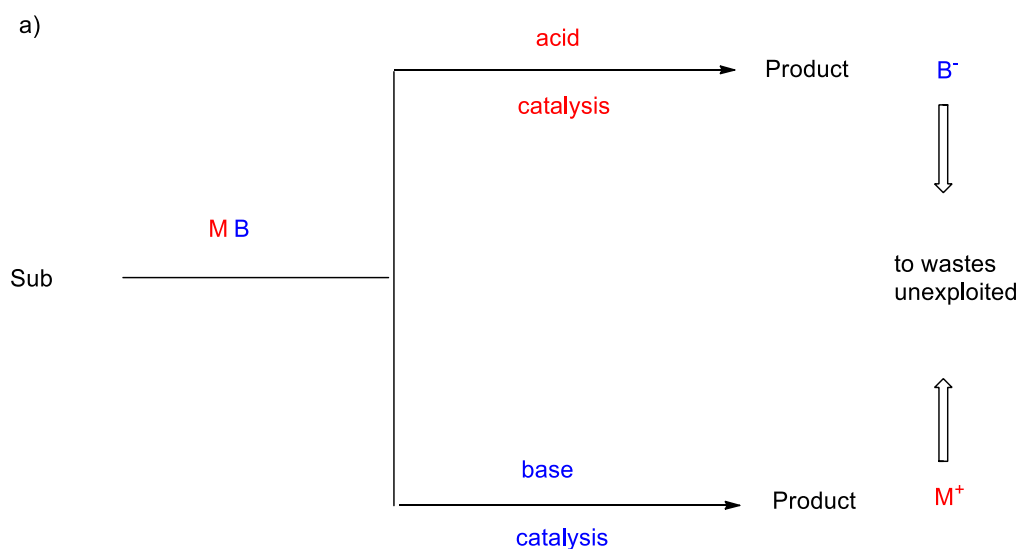
Product **2v** was isolated following **GP-5** as a brown solid (87%, 102.7 mg, 0.23 mmol) using **1v** (119.5 mg, 0.26 mmol) as reagent (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.84-7.78 (m, 3H), 7.73 (s, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.47-7.36 (m, 4H), 7.32-7.26 (m, 5H), 4.79 (d, J = 4.4 Hz, 2H), 2.40 (s, 3H), 1.84 (s, 3H), 1.61 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 198.6 (C=O), 143.3 (Cq), 142.2 (Cq), 138.2 (Cq), 138.1 (Cq), 134.2 (CH), 133.1 (Cq), 132.7 (Cq), 131.5 (Cq), 131.0 (Cq), 129.7 (2CH), 129.0 (2CH), 128.0 (CH), 127.6 (2CH), 126.6 (CH), 126.5 (2CH), 125.8 (CH), 122.4 (CH), 71.8 (Cq), 52.0 (CH₂), 29.0 (CH₃), 27.7 (CH₃), 21.6 (CH₃). **ESI-MS** calculated for C₂₈H₂₆NO₃S [M+H]⁺ 456.16, found 456.30. **ESI-HRMS** calculated for C₂₈H₂₆NO₃S [M+H]⁺ 456.1628, found 456.1630.

CHAPTER 2

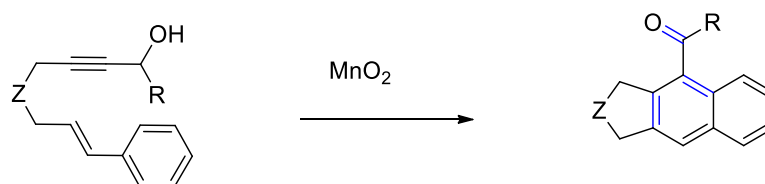
Mild dearomative Diels-Alder cyclizations via sequential catalysis

Introduction

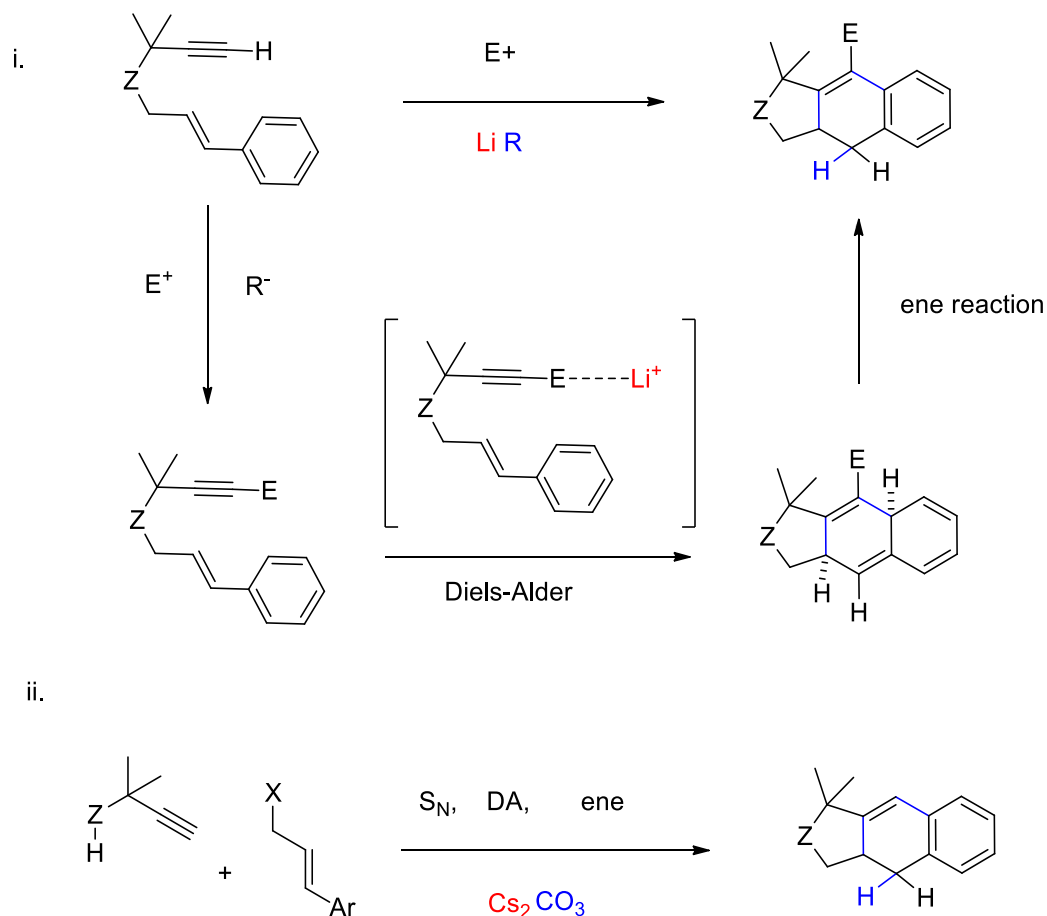
The use of acids or bases is very common in organic synthesis. They can exist in form of salt or complex and generally one of their two fragments is involved during a chemical transformation. The other fragment becomes a part of waste after completion of the reaction (Scheme 1, a). Herein we discuss a synthetic methodology in which we obtain complex molecules starting from well accessible substrates and employing both components of well known organic reagents such as organolithiums and carbonates. This work allowed us to obtain dihydronaphthalene derivatives through a sequential process which involves, first a nucleophilic substitution and then the alkali metal, released during the first process, catalyzes a dearomative Diels Alder reaction between an alkyne and a styrene moiety^{33,34} (Scheme 1c, i, ii). Many examples of Dearomative Diels Alder reactions for synthesis of bioactive molecules have been reported during the last decade employing transition metals¹⁸, thermal^{14,15} or microwave conditions.¹⁷ However they generally produced a mixture of dihydronaphthalenes and naphthalenes. Very recently our group reported a catalytic approach for the synthesis of naphthalene derivatives promoted by MnO_2 ,³⁵ a work discussed in the Chapter 1 (Scheme 1, b).



b) Previous work: sequential alcohol oxidation, dearomative 4+2 cycloaddition, aromatization



c) This work: sequential nucleophilic substitution, dearomative[4+2],ene



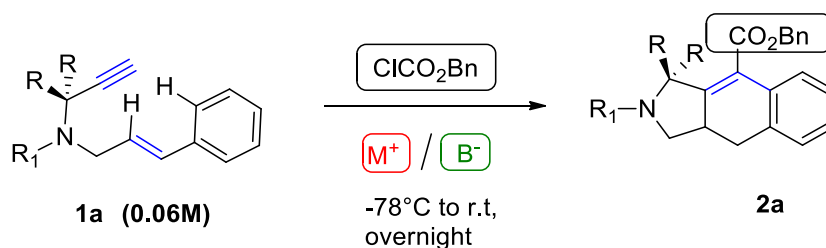
Scheme 1. The usual fate of ionic salt promoters vs the sequential catalysis approach

³³ L. L. Fluegel and T. R. Hoye, *Chem. Rev.*, **2021**, 121, 2413. ³⁴ W. Li, L. Zhou and J. Zhang, *Chem. Eur. J.*, **2016**, 22, 1158. ¹⁸ Mun, H. J.; Seong, E. Y.; Ahn, K. H.; Kang, E. J. *J. Org. Chem.* **2018**, 83, 1196–1203. ¹⁴ Klemm, L. H.; Gopinath, K. W. *Tetrahedron Lett.* **1963**, 4, 1243. ¹⁵ Chackalamannil, S., Doller, D., Eagen, K. *Tetrahedron Lett.* **2002**, 43, 5101–5103. ¹⁷ Kocsis, L. S., Kagalwala, H., N., Mutto, S., Godugu, B., Bernhard, S., Tantillo, D., J., Brummond, K., M. J. *Org. Chem.* **2015**, 80, 11686–11698. ³⁵ N. Camedda, M. Lanzi, F. Bigi, R. Maggi and G. Maestri, *Org. Lett.*, **2021**, 23, 6536.

Results and discussion

Enyne **1a** (0.3 mmol, 0.65 M in THF) was deprotonated in the presence of *n*-butyl lithium (titrated with I₂ before its use, 1.21 equiv) at -78°C under N₂ atmosphere. After 1 hour, we syringed slowly into the crude benzyl chloro formate (5 equiv.). Then the reaction was warmed up to room temperature and let it stir overnight. The next day, after quenching and purification by flash chromatography we recovered product **4a** in 58% yield.

Table 1. Optimization of the reaction conditions.



Entry ^a	Base	Yield of 2a (%) ^d	Entry ^a	Base	Yield of 2a (%) ^d
1^b	<i>n</i> -BuLi	58	6	MeMgBr	43
2	<i>n</i> -BuLi	66	7	<i>sec</i> -BuLi	14
3^c	<i>n</i> -BuLi	56	8	<i>tert</i> -BuLi	-
4	KHMDS	32	9	PhLi	72
5	LiHMDS	35	10	MeLi	82

a: reaction conditions: 0.3 mmol of **1a**, 0.65 M in THF, 1.2 equiv. of promoter, 2.5 equiv. of benzylchloroformate at -78 °C for 1 hour, then left warming overnight up to rt; **b:** with 5 equiv. of electrophile; **c:** with 1.2 equiv. of electrophile; **d:** isolated yields.

Reduction to 2.5 equiv of the electrophile. had a slight improvement to the yield. (entry 2, 66%). However a further decrease to 1.2 allowed an isolation of 56% yield (entry 3, Table 1). Amongst an array of organolithium reagents tested, *sec*-BuLi and *Tert*-BuLi were unsuccessful (entry 7-8, 14 % and 0% respectively). These results suggested us to employ reagents with lower basicity. The use of phenyl lithium, prepared *in situ*, gave us the first interesting result (entry 9, 72%). Trimethylsilyl amides such as KHMDS and LiHMDS were not reactive as PhLi (entry 4 and 5, 32% and 35%). Gratifyingly, the use of MeLi allowed us to achieve the highest yield of **2a** (entry 10, 82 %). With the conditions in our hands we extended the feasibility of this method to a variety of styryl-ynes (Figure 1). **2b** (81% yield) and **2c** (79% yield) were obtained by **1a** in the presence of phenyl chloroformate and ethyl chloroformate respectively. **1b** was scaled-up to 1 mmol, with a slight improvement of the yield (84%). Methyl-group in *para* position to the vinyl group in substrate **1e** allowed the formation of its corresponding cycle in 91 % yield. The same group in *ortho* position (substrate **1d**) decreased slightly the yield of **2d** (78%). The yield was slightly lower employing substrates bearing methoxy groups (**2f-h**). On the other hand -CF₃ had a detrimental impact into the yield of **2i** (41%). **2j** and **2k** were recovered in similar yield (69% and 68% respectively). Replacement of the phenyl groups with extended aromatic rings such as 1-

naphthyl and 2-naphthyl groups decreased the yield of the cycles (**2l-m**, 53% and 48%, respectively). It was worth noting that in cycle **2m** the functionalization occurred at the carbon in position 1 instead of the C-3 position. Steric hindrance produced by a cyclohexyl group at the propargyl moiety proved detrimental (**2n-o**, 43% and 26%, respectively), Mesityl group into the tether allowed the formation of products **2p** and **2q** in good yield (73% and 63%, respectively). Bulkier groups such as 2-naphthyl group proved suitable for the efficiency of the reaction (**2r**, 96%). Further extension of this methodology were represented by **2s**, **2t** and **2u** in which di-tert-butyl dicarbonate and *N,N*-dimethyl carbamyl chloride were used as electrophiles (34% and 64%, respectively).

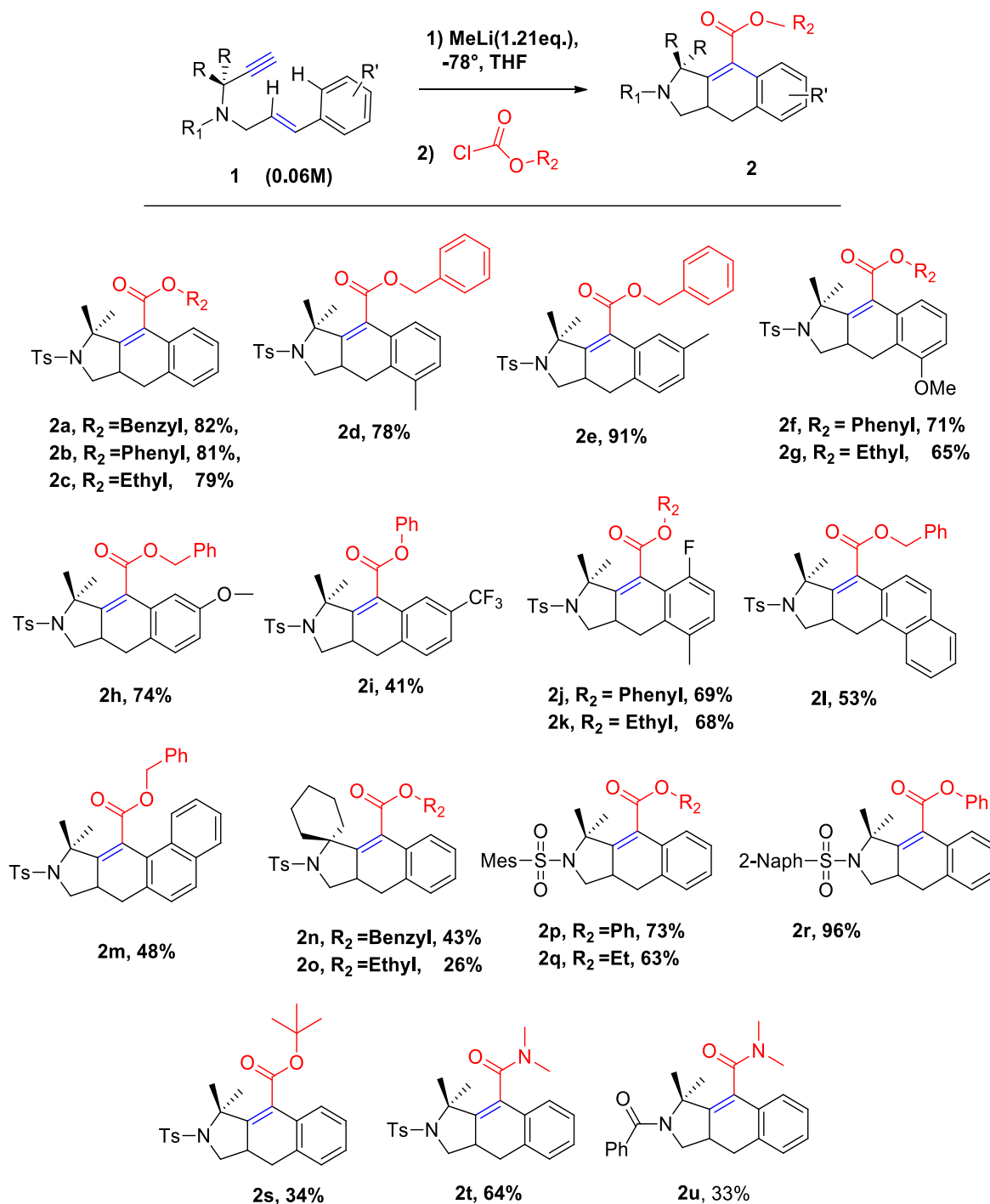
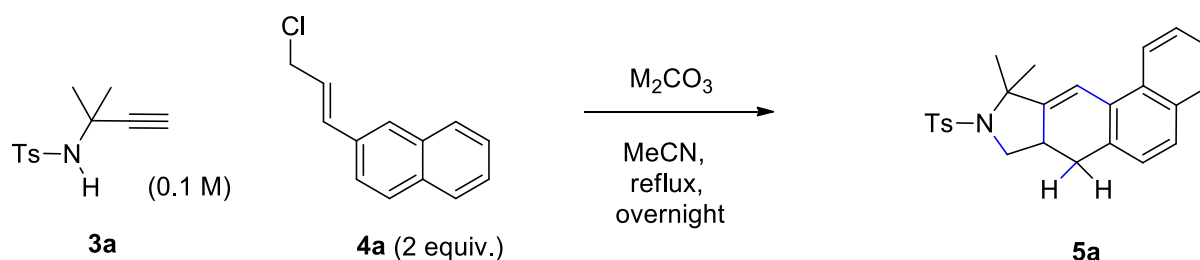


Figure 1. Synthesis of dihydronaphthalenes **2** promoted by methyl lithium; conditions as Table 1, entry 10.

Reagents without a disubstituted propargyl position were not compatible with this method.(see Limitations, experimental section) This confirms the Thorpe-Ingold effect produced by disubstituted ones, which seemed essential for promoting the described annulation.

2m was synthesized by **3a** and **4a** in presence of K_2CO_3 . Surprisingly the reaction produced traces of **5a**. The yield of **5a** increased to 65% warming the reaction up to 80°C in acetonitrile (Table 2, entry 1). Whereas Na_2CO_3 was inefficient (entry 2), anhydrous Cs_2CO_3 proved excellent in affording the cycle in excellent yield (93%, entry 4). The reaction was scaled-up to 1 mmol, albeit with diminished yield (50%).

Table 2. Optimization of reaction conditions with Carbonates



entry	M ₂ CO ₃ (4 eq)	Yield of 5a	entry	M ₂ CO ₃ (4 eq)	Yield of 5a
1	K ₂ CO ₃	Cycle (69%) Enyne (18%)	6^b	Cs ₂ CO ₃ (anhydrous)	Only enyne (95%)
2	Na ₂ CO ₃	No conversion	7	Ag ₂ CO ₃	No conversion
3	K ₂ CO ₃ (anhydrous)	Cycle 65 %	8	NaOAc (anhydrous)	No conversion
4	Cs ₂ CO ₃ (anhydrous)	93 % cycle	9	CsOAc (anhydrous)	No conversion
5^a	Cs ₂ CO ₃	85 % cycle	10^c	Cs ₂ CO ₃ (anhydrous)	Cycle 53%

a The reaction was stirred at reflux for two days. **b** The reaction was conducted at ambient temperature. **c** With 1.3 equiv. of **4**

Then we extended the efficacy of this method to a variety of propargylammides and chlorides in order to deliver thier corresponding cycles (Figure 2). Different aromatic systems such as 1-naphthyl and 9-anthracene proved tolerant to this approach (**5b-c**). Thiophene displayed a good reactivity (**5d**, 73%).The presence of a cyclohexyl group at the propargyl fragment decreased the yield (**7e**, 40%). Bulkier groups such as 2-naphthalene and mesityl group into the tether afforded their corresponding products in excellent yield (**5g-h**).

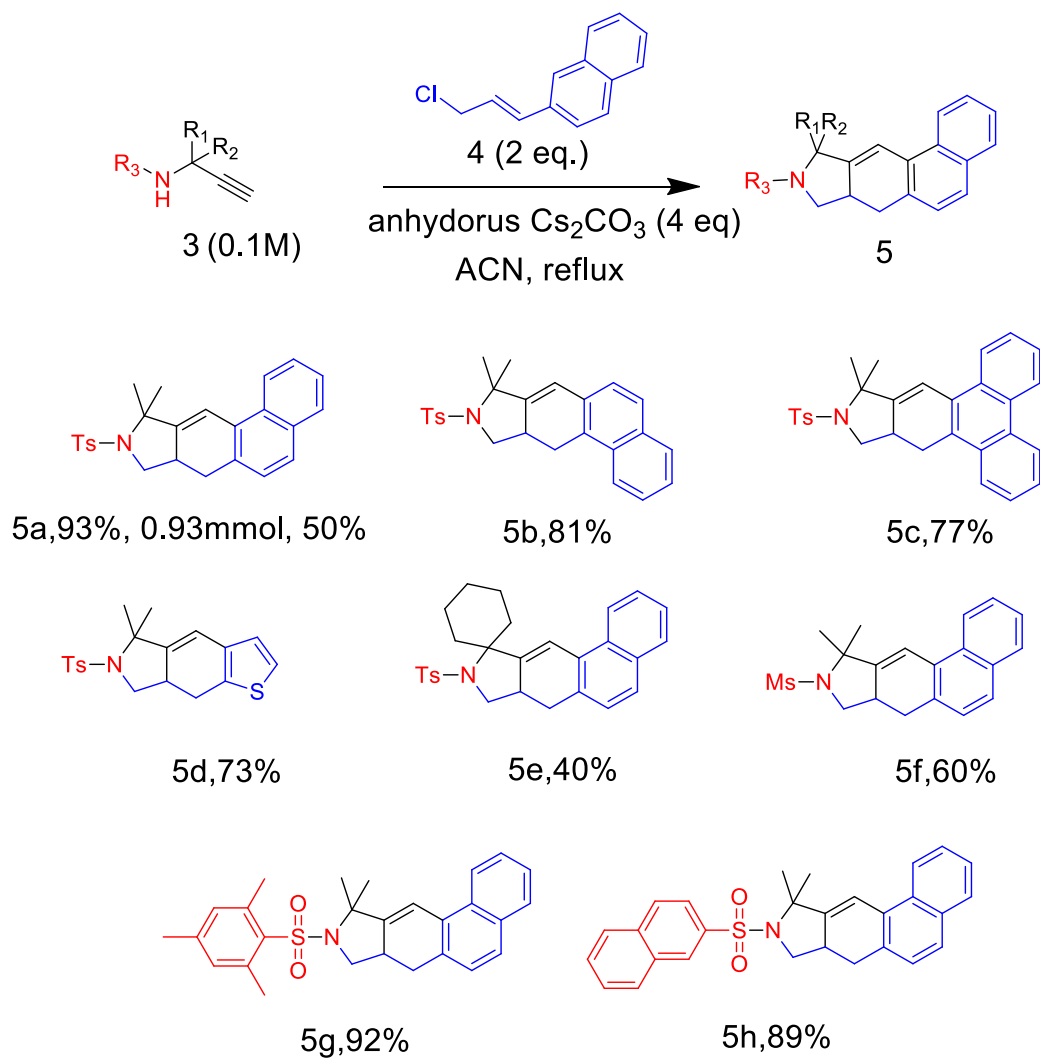
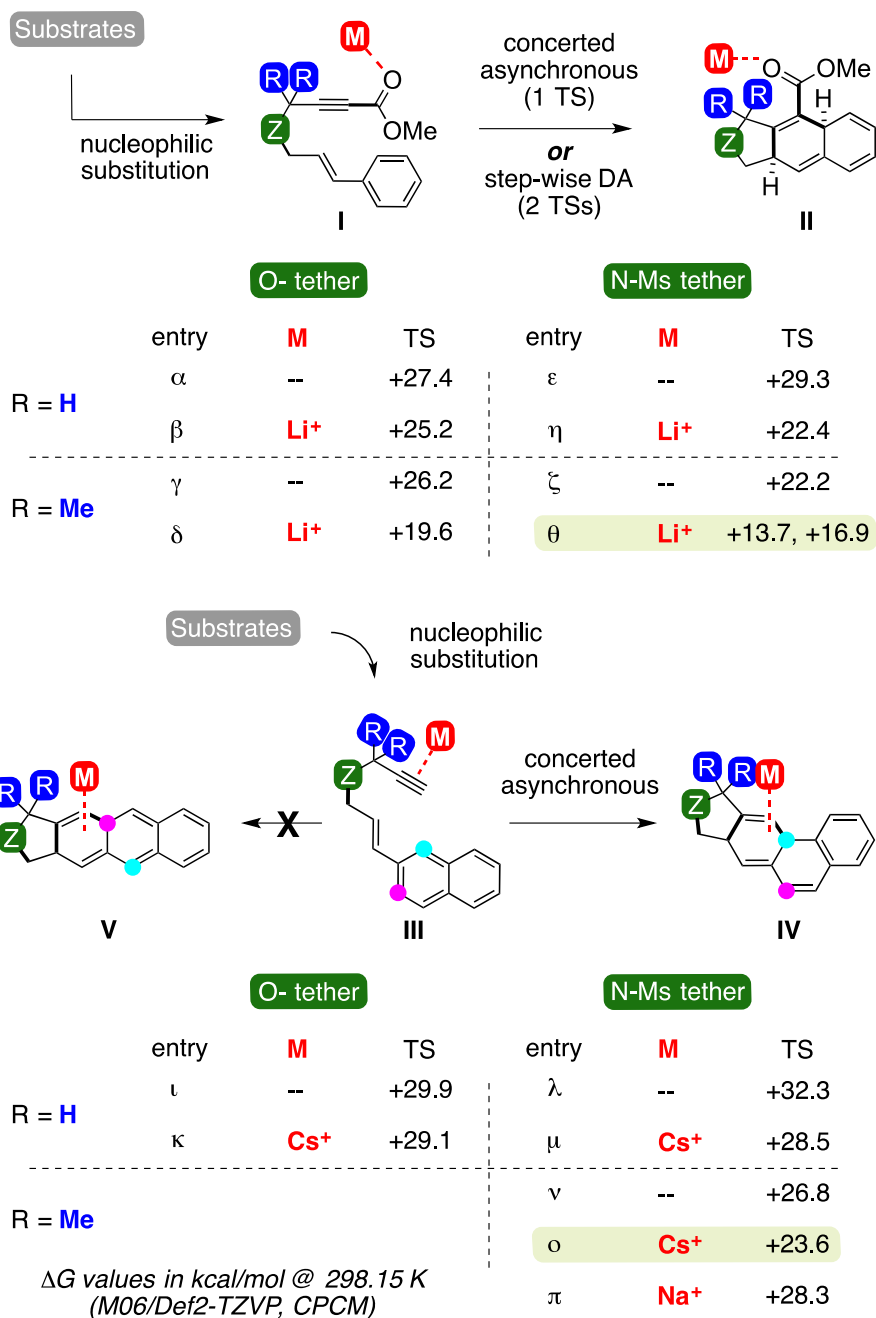


Figure 2. Sequential synthesis of fused polycycles **5** (0.3 mmol scale, isolated yield)

DFT calculations were carried out in order to investigate the reaction mechanism (Scheme 2). We considered 15 models of reaction analyzing the nature of propargyl substituents, alkali cations and tether groups (Scheme 2).



Scheme 2. Proposed mechanistic rationale and DFT modelling data.

According to experiments with MeLi, polarized substrates are essential in the dearomative cyclization. We assumed that a carbonyl/lithium coordination is essential for promoting the annulation (**I**, Scheme 2). The yield of **2** was lower when BOC-anhydride was used (product **2s**, see the scope) because maybe the carboxylate coproduct would bind lithium more efficiently than the ester group (**I**). Finally mild conditions and lack of oxidants or oxygen makes **II** undergo ene-reaction delivering finally **2**. The energy barriers related to dearomative cyclisations in presence of an alkali metal were lower compared to those of uncatalyzed ones. However the energy barriers are remarkably high for unsubstituted substrates at the propargyl moiety and with O tethers. This is consistent with the limitations (See experimental section). Only θ propiolates among the others follows a stepwise mechanism. In this case the energy barrier was below 20 kcal/mol compared to the other propiolates. We can now summarize the reaction mechanism (Figure 3). After deprotonation promoted by MeLi and subsequent electrophilic substitution substrate **1** affords the intermediate **A** which next undergoes cyclization via Li-carbonyl coordination producing **B**. Afterwards **B** undergoes another cyclization affording **C**, which produces the desired product **2** via *ene-reaction* (Figure 3 and Figure 5 for *ene reaction*).

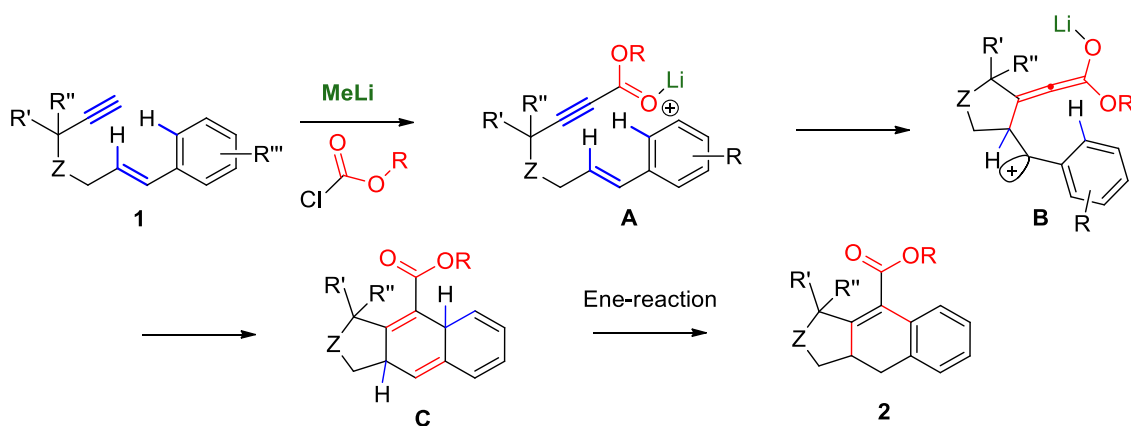


Figure 3. Reaction mechanism of Diels-Alder/ene-reaction promoted by MeLi

In the case of cesium carbonate, the functionalization of 2-naphthyl arms can be rationalized by the Diels-Alder cyclization of **III** in the scheme 2. In fact the aromaticity of one ring is preserved by cyclization on C(sp²)-H at position 1 (compound **IV**), but the aromaticity of two rings would be lost if cyclisation occurred at C3 position (in pink, compound **V**). This is consistent with the obtainment of products **5a**, **5e-f**, **5g-h**. Enyne **III** (see Scheme 1) displayed a concerted mechanism because there is not polarization at the alkyne moiety. The reactions showed a lower energetic barrier when enyne **III** features disubstitution at the propargyl moiety and is characterized by a rigid N-tether group. However it can furnish **IV** only in the presence of Cs⁺ *via* cation- π interaction (**IIIo**, scheme 1). Na⁺ is incapable of providing **IV**, and its value in ΔG is comparable to those of uncatalyzed ones. The reaction mechanism can be described in this way: Upon S_N2 reaction promoted by Cs₂CO₃, the reaction affords the intermediate **A'**. Then It undergoes cyclization trough Cs⁺-alkyne moiety interaction affording cycle **B'** *via* concerted mechanism. At the end **B'** produces **5** through *ene reaction* (Figure 4, Figure 5 for *ene-reaction*).

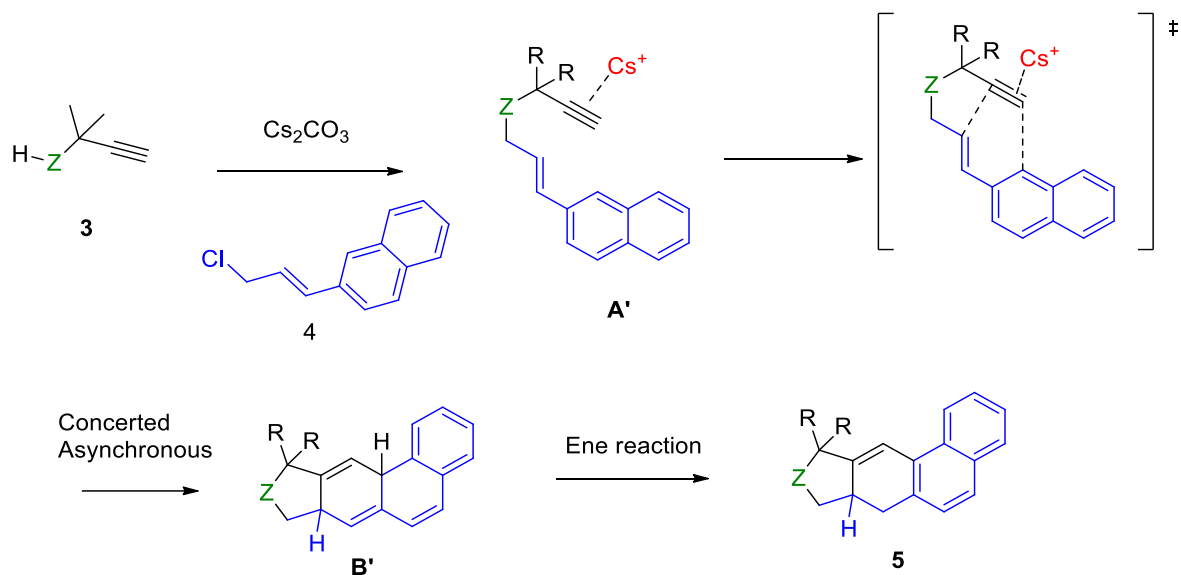


Figure 4. Reaction mechanism of Diels-Alder/ene-reaction promoted by Cs_2CO_3

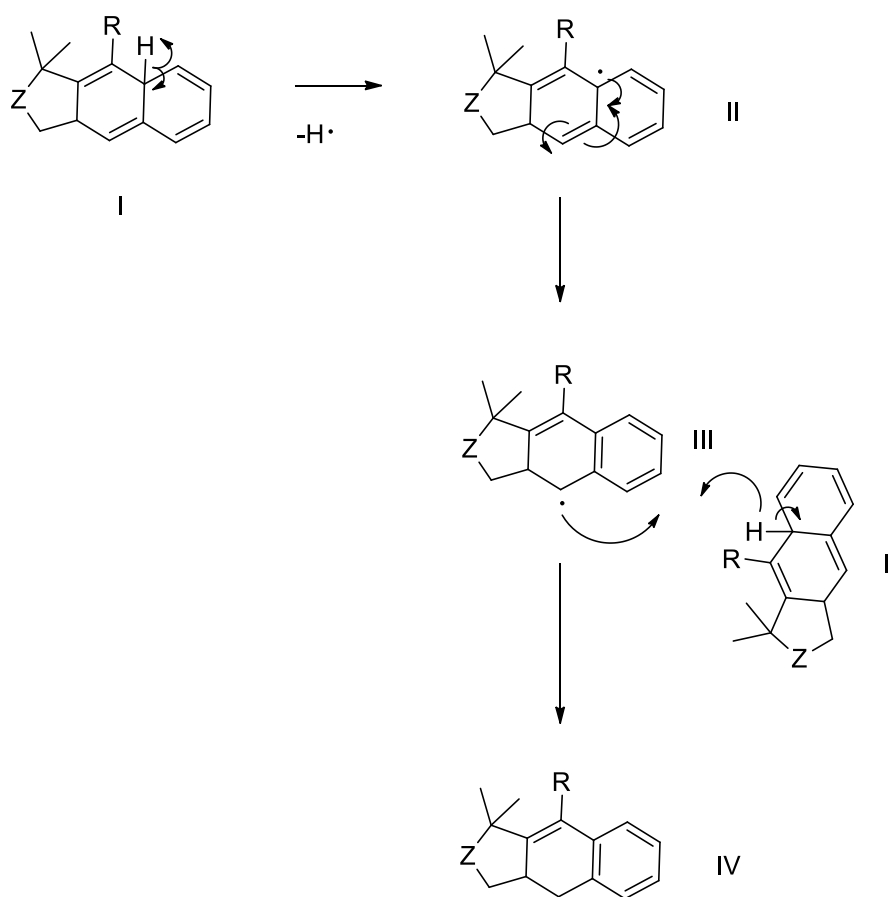


Figure 5. Mechanism of the formal *ene*-reaction

Finally we concluded this work performing other reactions as examples of post-functionalizations. Cycle **2a** in presence of 40 equiv. of MnO_2 afforded a mixture of aromatized products **2v** and **2v'**, isolated respectively in 44% and 22%. Moreover reaction of **2b** in the presence of chloro perbenzoic acid provided cycle **5i** in 41% of yield (Figure 6)

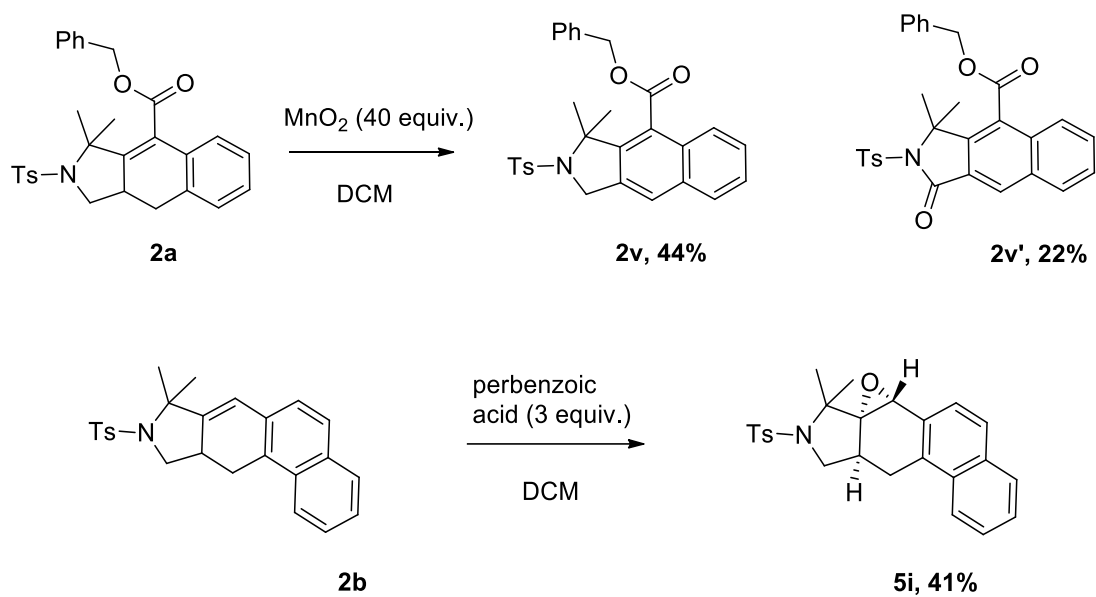


Figure 6. Post-functionalizations

Conclusion

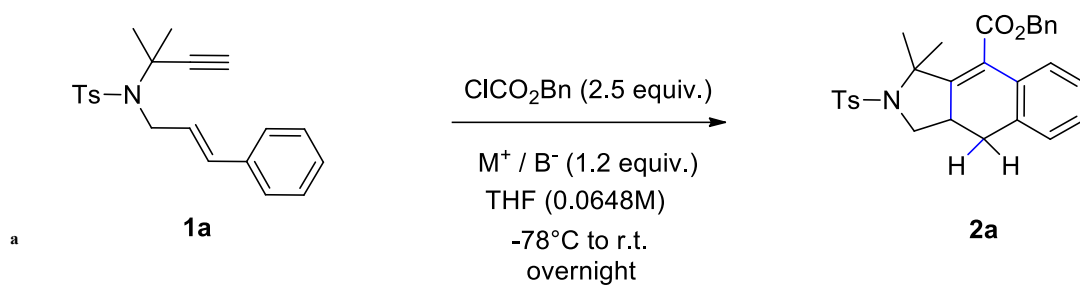
We described a catalytic method which enabled the formation of fused polyheterocycles with a dihydronaphthalene core. This was performed employing substrates with a vinylarene and an alkyne arm, providing a selective dearomative Diels-Alder/aromatization rearrangement process. This synthetic practical approach enables the formation of products in high yields under friendly conditions. The reaction serves as a proof-of-concept for studying in the future sequential cascades using basic alkali derivatives as promoters. DFT calculations provided fresh insights into the the variables influencing the dearomative Diels-Alder cyclization.

Experimental section

General remarks

Unless otherwise noted, reagents and solvents were purchased from commercial sources and used as received without further purification. MeLi used for cyclizations was in solution 3.1 M in diethoxymethane. Cs₂CO₃ used for the other cyclizations was in powder form, synthetic grade (99%). Dry solvents used for the preparation of substrates were prepared by passing them through alumina columns using an Inert® systems and were stored under nitrogen. Chromatographic purifications were performed under gradient using a Combiflash® system and prepacked disposable silica cartridges or through isocratic flash chromatography using commercial 60 Å silica gel. All reactions that required heating were performed with the use of high-vacuum grade silicon oil as heating transfer agent. ¹H and ¹³C NMR spectra were recorded at 300 K on a Bruker 400 MHz spectrometer using solvents as internal standards (7.26 ppm for ¹H NMR and 77.04 ppm for ¹³C NMR for CDCl₃). ¹⁹F NMR spectra were recorded at 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. Reported assignments were based on COSY, HSQC and HMBC correlation experiments. LC-MS were recorded on an Agilent LQ Mass Spectrometer (ESI source). High-resolution mass analyses were recorded on a LTQ ORBITRAP XL Thermo Mass Spectrometer (Electrospray source).

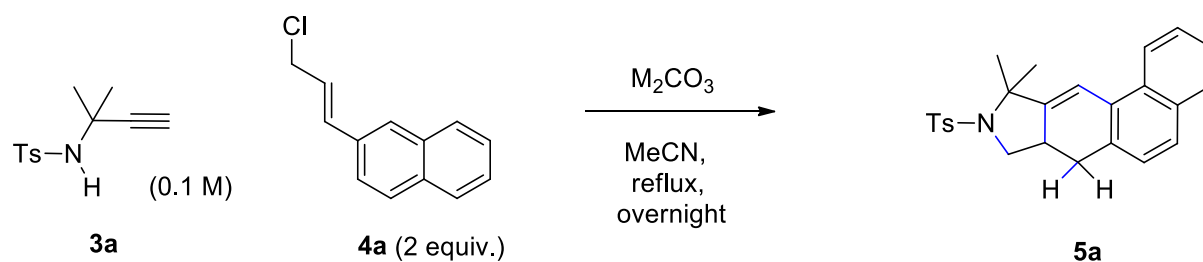
Optimization of reaction conditions with organolithium reagents



entry	Salt (1.2 equiv.)	Yield of 2a (%)	entry	Salt (1.2 equiv.)	Yield of 2a (%)
1^a	n-BuLi	58%	9	MeLi	82%
2	n-BuLi	66 %	10	MeMgBr	43%
3^b	n-BuLi	56 %	11	Tert-BuLi	1a decomposition
4^c	n-BuLi	57%	12	Sec-BuLi	14%
5^d	n-BuLi	27%	13	PhLi	72%
6	NaH	No conversion	14	p-CF ₃ -PhLi	52%
7	KHMDS	32%	15	p-MeO-PhLi	63%
8	LiHMDS	35%	16^e	MeLi	45%

a with 5 equiv. of benzyl chloroformate. **b** with 1.25 equiv. of benzyl chloroformate. **c** The reaction was firstly cooled at -78°C and after 1 hour warmed and stirred overnight at 40°C. **d** The reaction was firstly cooled at -78°C and stirred for two days at 0°C. **e** The reaction was conducted in diethyl ether.

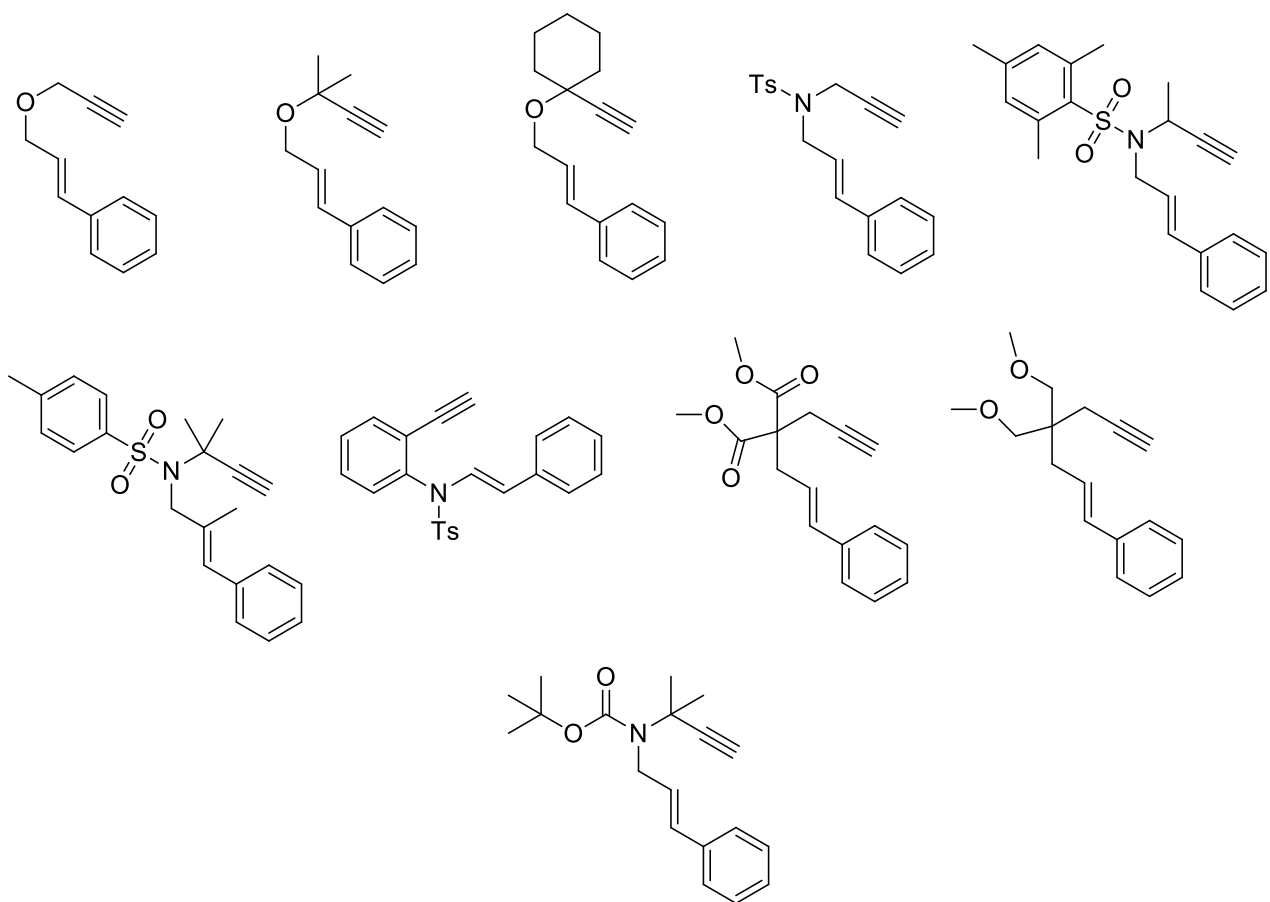
Optimization of reaction conditions with Cesium



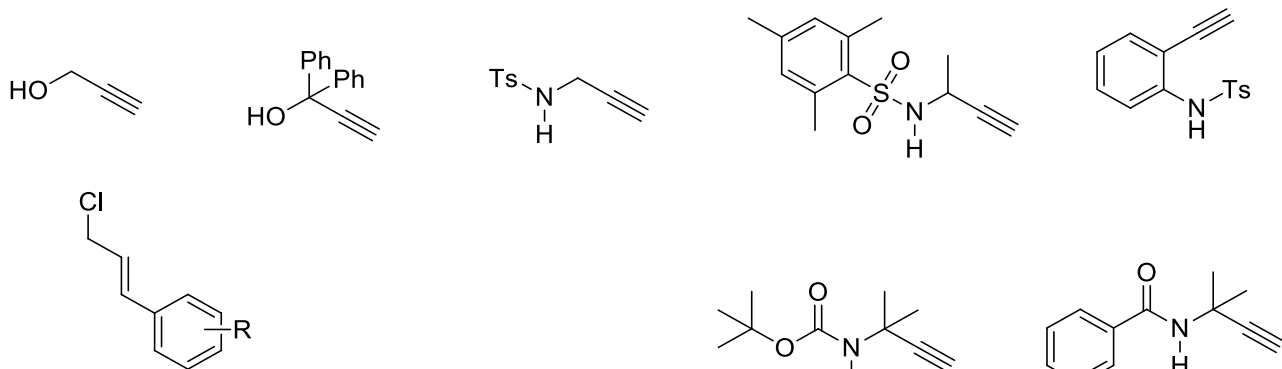
entry	M_2CO_3 (4 eq)	Yield of 5a	entry	M_2CO_3 (4 eq)	Yield of 5a
1	K_2CO_3	Cycle (69%) Enyne (18%)	6^b	Cs_2CO_3 (anhydrous)	Only enyne (95%)
2	Na_2CO_3	No conversion	7	Ag_2CO_3	No conversion
3	K_2CO_3 (anhydrous)	Cycle 65 %	8	$NaOAc$ (anhydrous)	No conversion
4	Cs_2CO_3 (anhydrous)	93 % cycle	9	$CsOAc$ (anhydrous)	No conversion
5^a	Cs_2CO_3	85 % cycle	10^c	Cs_2CO_3 (anhydrous)	Cycle 53%

a The reaction was stirred at reflux for two days. **b** The reaction was conducted at ambient temperature. **c** With 1.3 equiv. of **4a**

Limitations MeLi



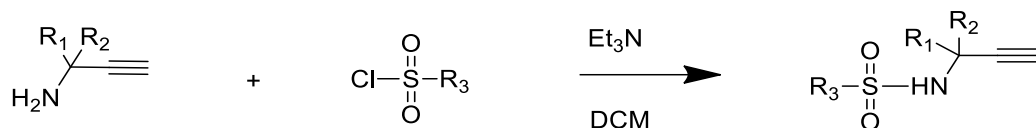
Limitations Cs_2CO_3



R: Electron rich or electron withdrawing group

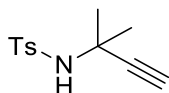
Synthesis of reagents

General procedure for the synthesis of benzenesulfonamides (GP-1)



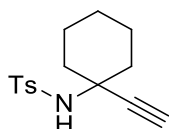
The reaction was carried out following the literature³⁵. To a mixed solution of propargylamine (1 equiv.) and Et₃N (2 equiv.) in anhydrous dichloromethane (0.3 M) was slowly added the sulfonyl chloride (1.2 equiv.) at 0 °C. Then the resulting mixture was stirred overnight at room temperature until completion. Once finished, the reaction mixture was washed in sequence with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude product was concentrated under reduced pressure, solubilized with ethyl acetate and the desired product was recovered either by crystallization achieved by the addition of hexane or isolated by flash chromatography (hexane:ethyl acetate 8:2).

4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (3a)



Product **3a** was isolated following **GP-1** as a white solid (63 %, 1801 mg, 7.59 mmol) using 2-methylbut-3-yn-2-amine (1000 mg, 12.0 mmol) and 4-methylbenzene-1-sulfonyl chloride (2522 mg, 13.2 mmol) as reagents (crystallization). All the data spectra are reported in the literature³⁶. ¹H NMR (400 MHz, CDCl₃) δ = 7.80 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 5.38 (s, 1H), 2.40 (s, 3H), 2.06 (s, 1H), 1.52 (s, 6H)..

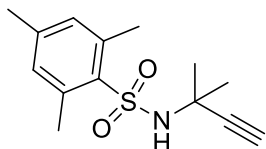
N-(1-ethynylcyclohexyl)-4-methylbenzenesulfonamide (3e)



Product **3e** was isolated following **GP-1** as a brown solid (32 %, 729 mg, 2.6 mmol) using 1-ethynylcyclohexanamine (1000 mg, 8.12 mmol) and 4-methylbenzene-1-sulfonyl chloride (1857 mg, 9.74 mmol) as reagents (eluent: hexane:EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ = 7.80 (d, *J* = 8.4

Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 5.13-5.10 (brs, 1H), 2.41 (s, 3H), 2.11 (s, 1H), 2.01-1.98 (m, 2H), 1.67-1.49 (m, 8H). All the data spectra are reported in the literature ³⁶.

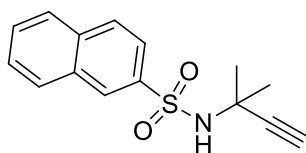
2,4,6-trimethyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (**3g**)



Product **3g** was isolated following **GP-1** as a white solid (49 %, 1292 mg, 4.9 mmol) using 2-methylbut-3-yn-2-amine (830 mg, 10 mmol) and 2,4,6-trimethylbenzene-1-sulfonyl chloride (2624 mg, 12 mmol) as reagents (eluent: hexane:EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ = 6.93 (s, 2H), 4.93 (s, 1H), 2.66 (s, 6H), 2.29 (s, 3H), 2.08 (s, 1H), 1.53 (s, 6H). All the data spectra are reported in the literature ³⁶.

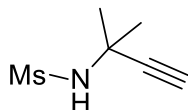
³⁶ Liu, R.; Chou, Y.; Lian, B.; Fang, D.; Gao, M.; Cheng, Liu, G. *Org. Lett.* **2019**, 21, 6815–6820

N-(2-methylbut-3-yn-2-yl)naphthalene-2-sulfonamide (**3h**)



Product **3h** was isolated following **GP-1** as a white solid (63 %, 862 mg, 3.1 mmol) using 2-methylbut-3-yn-2-amine (415 mg, 5 mmol) and naphthalene-2-sulfonyl chloride (1360 mg, 6 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.50 (s, 1H), 7.97-7.88 (m, 4H), 7.65-7.57 (m, 2H), 5.07 (s, 1H), 1.97 (s, 1H), 1.58 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 138.5 (Cq), 134.8 (Cq), 132.0 (Cq), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 127.9 (CH), 127.4 (CH), 123.0 (CH), 85.3 (Cq), 71.3 (CH), 50.1 (Cq), 30.8 (2CH₃). **ESI-MS** calculated for C₁₅H₁₅NNaO₂S [M+Na]⁺ 296.07, found 296.14.

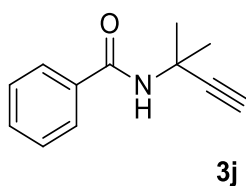
N-(2-methylbut-3-yn-2-yl)methanesulfonamide (**3i**)



Product **3i** was isolated following **GP-1** as a white solid (88 %, 1711 mg, 10.6 mmol) using 2-methylbut-3-yn-2-amine (1000 mg, 12 mmol) and methanesulfonyl chloride (1656 mg, 14 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 5.10 (s, 1H), 3.14 (s, 3H), 2.49 (s, 1H), 1.60 (s, 6H). All the data spectra are reported in the literature ³⁷.

³⁷Liu, R.; Ni, Z.;Giordano, L.; Tenaglia, A. *Org. Lett.* **2016**, 18, 4040–4043

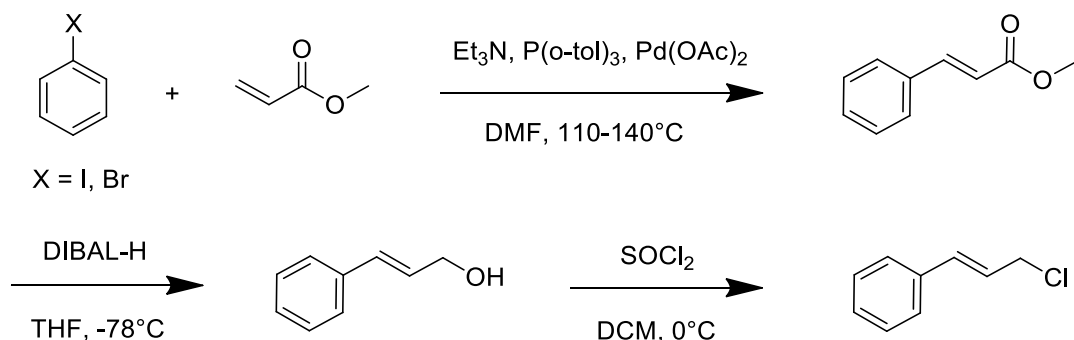
N-(2-methylbut-3-yn-2-yl)benzamide (**3j**)



Product **3j** was isolated following **GP-1** as a white solid (96 %, 379 mg, 2.0 mmol) using 2-methylbut-3-yn-2-amine (1000 mg, 12 mmol) and benzoyl chloride (351 mg, 2.5 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.77-7.74 (m, 2H), 7.51-7.47 (m, 1H), 7.44-7.40 (m, 2H), 6.21 (s, 1H), 2.39 (s, 1H), 1.77 (s, 6H). All the data spectra are reported in the literature ³⁸

³⁸ Smedley, C.J.; Barrow, A.S.; Spiteri, C.; Giel, M.C.; Sharma, P.; Moses, J.E. *Chem. Eur. J.* **2017**, 23, 9990–9995.

General procedure for the synthesis of (E)-(3)-chloropropenes (GP-2)



Heck coupling reaction

In a solution of the halide (1 equiv.) in DMF (0.2 M) under nitrogen condition were added methyl malonate (1.2 equiv.), triethylamine (3 equiv.), tri-*o*-tolyl phosphine (0.1 equiv.) and palladium acetate (0.05 equiv.). The mixture was stirred overnight at 110-140°C until total completion. Once finished, the organic layer was extracted with ethyl acetate and washed in sequence with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The desired product was isolated by the flash chromatography (hexane:ethyl acetate 8:2)

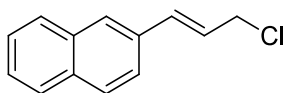
Preparation of the alcohols

In a Schlenk tube a solution of the alcohol (1 equiv.) in THF (0.25 M) was prepared under nitrogen condition. The mixture was cooled to -78°C. Then a solution of DIBAL-H (1M in toluene, 2.3 equiv.) was slowly added dropwise to the solution. The resulting mixture was stirred at -78°C for half an hour and monitored by TLC. Once finished, the reaction was quenched with a saturated solution of NH_4Cl until bubbles vanished completely and 1-2 ml of 10% HCl aqueous solution were added. The resulting mixture was stirred for other 30 minutes. The organic layer was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The desired product was recovered by flash chromatography (hexane:ethyl acetate 8:2 $\rightarrow$ 3:2).

Preparation of chlorides

The reaction was carried out following the literature ³⁹. A solution of the alcohol (1 equiv.) at 0°C in DCM (0.5 M) was prepared. The Thionyl chloride (1.2 equiv.) was added slowly dropwise and the resulting solution was stirred and monitored by TLC. When the reaction is completed the crude was quenched with a saturated solution of NaHCO₃ until bubbles vanished completely. The organic layer was extracted with dichloromethane, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude was extracted again with hexane, washed with brine and dried over Na₂SO₄. The crude was concentrated under reduced pressure in order to afford the desired chloride.

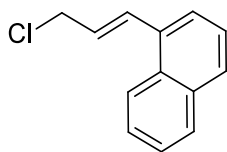
(E)-2-(3-chloroprop-1-en-1-yl)naphthalene (4a)



Product **4a** was isolated following **GP-2** as a white solid (87 %, 353 mg, 1.7 mmol) using (E)-3-(naphthalen-2-yl)prop-2-en-1-ol (370 mg, 2 mmol) as reagent. ¹H NMR (400 MHz, CDCl₃) δ = 7.82-7.79 (m, 3H), 7.76 (s, 1H), 7.60 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.49-7.46 (m, 2H), 6.82 (d, *J* = 15.6 Hz, 1H), 6.45 (dt, *J* = 15.6, 7.2 Hz, 1H), 4.31 (dd, *J* = 7.2, 1.2 Hz, 2H). All the data spectra are reported in the literature ³⁹

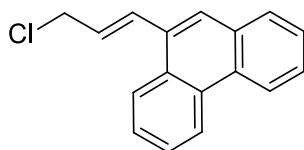
³⁹Jette, C. I.; Tong, Z. J.; Hadt R. G.; Stoltz, B. *Angew. Chem. Int. Ed.* **2020**, 59, 2033–2038.

(E)-1-(3-chloroprop-1-en-1-yl)naphthalene (4b)



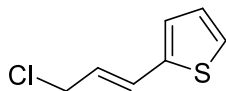
Product **4b** was isolated following **GP-2** as a white solid (80 %, 408 mg, 2.0 mmol) using (E)-3-(naphthalen-1-yl)prop-2-en-1-ol (468 mg, 2.5 mmol) as reagent. All the data spectra are reported in the literature ³⁹. **¹H NMR** (400 MHz, CDCl₃) δ = 8.10 (d, J = 8.3 Hz, 1H), 7.87 (dd, J = 8.0, 1.6 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 6.2 Hz, 1H), 7.56-7.41 (m, 4H), 6.37 (dt, J = 15.4, 7.1 Hz, 1H), 4.36 (dd, J = 7.1, 1.3 Hz, 2H).

(E)-9-(3-chloroprop-1-en-1-yl)phenanthrene (4c)



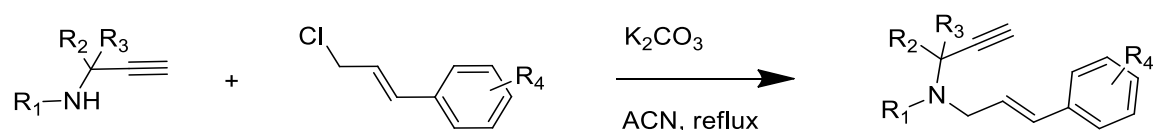
Product **4c** was isolated following **GP-2** as a white solid (76 %, 192 mg, 0.76 mmol) using (E)-3-(phenanthren-9-yl)prop-2-en-1-ol (235 mg, 1 mmol) as reagent. **¹H NMR** (400 MHz, CDCl₃) δ = 8.73 (dd, J = 7.9, 1.6 Hz, 1H), 8.66 (d, J = 6.9 Hz, 1H), 8.12 (dd, J = 8.0, 1.5 Hz, 1H), 7.89 (dd, J = 7.6, 1.6 Hz, 1H), 7.84 (s, 1H), 7.71-7.58 (m, 4H), 7.42 (d, J = 14.0 Hz, 1H), 6.44 (dt, J = 15.3, 7.0 Hz, 1H), 4.39 (dd, J = 7.1, 1.3 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ = 132.6 (Cq), 131.9 (CH), 131.6 (Cq), 130.4 (3Cq), 128.8 (CH), 128.5 (CH), 126.9 (CH), 126.8 (2CH), 126.7 (CH), 125.4 (CH), 124.5 (CH), 123.2 (CH), 122.6 (CH), 45.4 (CH₂). **ESI-MS** calculated for C₁₇H₁₃ClK [M+K]⁺ 291.03, found 291.31.

(E)-2-(3-chloroprop-1-en-1-yl)thiophene (4d)



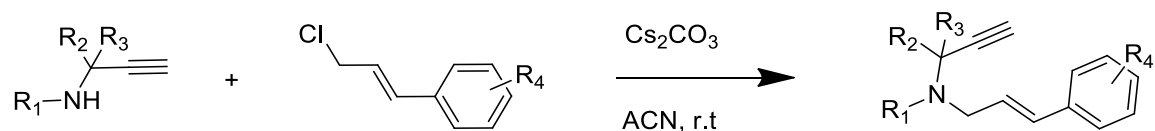
Product **4d** was isolated following **GP-2** as a white solid (78 %, 143 mg, 0.90 mmol) using (E)-3-(thiophen-2-yl)prop-2-en-1-ol (163 mg, 1.2 mmol) as reagent. **¹H NMR** (400 MHz, CDCl₃) δ = 7.20 (d, J = 0.9 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.98 (dd, J = 5.0, 3.6 Hz, 1H), 6.79 (d, J = 15.4 Hz, 1H), 6.16 (dt, J = 15.5, 7.2 Hz, 1H), 4.21 (dd, J = 7.2, 1.2 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ = 140.8 (Cq), 127.5 (CH), 127.3 (CH), 126.8 (CH), 125.3 (CH), 124.2 (CH), 45.3 (CH₂). **ESI-MS** calculated for C₇H₇ClNaS [M+Na]⁺ 180.99, found 180.16.

General procedure for the synthesis of enynes (GP-3)



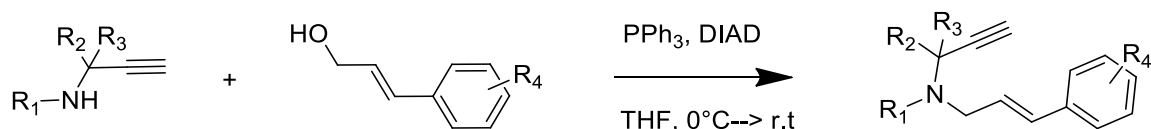
In a schlenk tube a solution of propargilamide (1 equiv.) in acetonitrile (0.1 M) was prepared. Then K₂CO₃ (4 equiv.) was added to the solution. Finally a solution of Cynnamil chloride (2 equiv.) was syringed to the resulting mixture. The reaction was refluxed at 80°C and monitored by TLC until completion. Once finished, the organic layer was extracted with ethyl acetate, washed with brine and dried over Na₂SO₄. The crude was concentrated under reduced pressure and the desired product was isolated by flash cromatography (Hexane: Ethyl acetate 8:2).

General procedure for the synthesis of enynes (GP-4)



In a schlenk tube a solution of propargilamide (1 equiv.) in acetonitrile (0.1 M) was prepared. Then Cs₂CO₃ (4 equiv.) was added to the solution. Finally a solution of Cynnamil chloride (2 equiv.) was syringed to the resulting mixture. The reaction was stirred at ambient temperature and monitored by TLC until completion. Once finished, the organic layer was extracted with ethyl acetate, washed with brine and dried over Na₂SO₄. The crude was concentrated under reduced pressure and the desired product was isolated by flash cromatography (Hexane: Ethyl acetate 8:2).

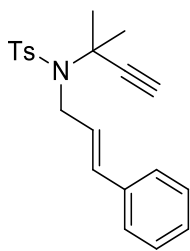
General procedure for the synthesis of enynes (GP-5)



The reaction was carried out following the literature³⁵. PPh₃ (typically 3 mmol, 1.5 equiv.) and 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (typically, 2.0 mmol, 1.0 equiv.) were sequentially added to a solution of the desired allyl alcohol (typically, 2.2 mmol, 1.1 equiv.) in dry THF (0.3 M). The mixture was cooled to 0 °C and DIAD (typically, 3 mmol, 1.5 equiv.) was added dropwise. The resulting mixture was stirred at room temperature until complete conversion of the sulfonamide, which was monitored by TLC. Hence, the solution was concentrated under reduced pressure and purified by flash chromatography (isocratic nHexane/EtOAc 95:5) to afford the desired product

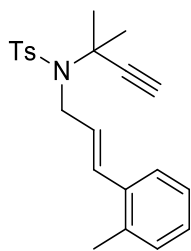
³⁵ N.Camedda, M. Lanzi, F. Bigi, R. Maggi and G. Maestri, *Org. Lett.*, **2021**, 23, 6536.

N-cinnamyl-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (1a)



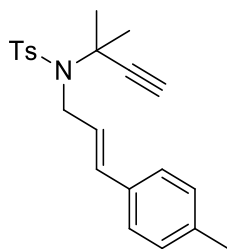
Product **1a** was isolated following **GP-3** as a white solid (69 %, 721 mg, 2.0 mmol) using **3a** (700 mg, 2.9 mmol) and (E)-(3-chloroprop-1-en-1-yl)benzene (900 mg, 5.9 mmol) as reagents (eluent: hexane:EtOAc = 8:2). All the data spectra are reported in the literature³⁵. **¹H NMR** (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.3 Hz, 2H), 7.39-7.37 (m, 2H), 7.34-7.30 (t, J = 7.4 Hz, 2H), 7.26-7.24 (m, 3H), 6.56 (d, J = 16.0 Hz, 1H), 6.38 (dt, J = 15.9, 6.3 Hz, 1H), 4.35 (dd, J = 6.3, 1.4 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 1H), 1.72 (s, 6H).

(E)-4-methyl-N-(2-methylbut-3-yn-2-yl)-N-(3-(o-tolyl)allyl)benzenesulfonamide (1b)



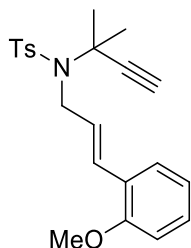
Product **1b** was isolated following **GP-3** as a white solid (93 %, 346 mg, 0.94 mmol) using **3a** (239 mg, 1.0 mmol) and (E)-1-(3-chloroprop-1-en-1-yl)-2-methylbenzene (337 mg, 2.0 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.77 (d, J = 8.3 Hz, 2H), 7.45-7.41 (m, 1H), 7.27-7.25 (m, 2H), 7.19-7.14 (m, 3H), 6.81 (d, J = 16.0 Hz, 1H), 6.25 (dt, J = 15.8, 6.3 Hz, 1H), 4.37 (dd, J = 6.3, 1.4 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 1H), 2.33 (s, 3H), 1.73 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.0 (Cq), 139.9 (Cq), 136.0 (Cq), 135.5 (Cq), 130.6 (CH), 130.2 (CH), 129.4 (2CH), 129.2 (CH), 127.5 (CH), 127.3 (2CH), 126.1 (CH), 125.8 (CH), 86.5 (Cq), 72.1 (CH), 56.5 (Cq), 50.4 (CH₂), 30.7 (2CH₃); 21.5 (CH₃), 19.8 (CH₃). **ESI-MS** calculated for C₂₂H₂₅NNaO₂S [M+Na]⁺ 390.15, found 390.28

(E)-4-methyl-N-(2-methylbut-3-yn-2-yl)-N-(3-(p-tolyl)allyl)benzenesulfonamide (1c)



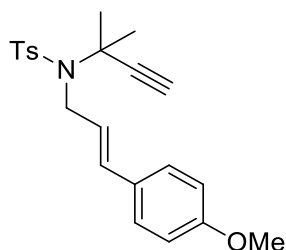
Product **1c** was isolated following **GP-3** as a white solid (98 %, 215 mg, 0.58 mmol) using **3a** (141 mg, 0.60 mmol) and (E)-1-(3-chloroprop-1-en-1-yl)-4-methylbenzene (200 mg, 1.2 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.3 Hz, 2H), 7.29-7.24 (m, 4H), 7.13 (d, J = 7.9 Hz, 2H), 6.53 (d, J = 15.9 Hz, 1H), 6.33 (dt, J = 15.9, 6.3 Hz, 1H), 4.34 (dd, J = 6.4, 1.4 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 1H), 2.35 (s, 3H), 1.71 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 142.9 (Cq), 139.9 (Cq), 137.5 (Cq), 134.0 (Cq), 132.4 (CH), 129.4 (2CH), 129.3 (2CH), 127.3 (2CH), 126.9 (CH), 126.4 (CH), 86.5 (Cq), 72.0 (CH), 56.5 (Cq), 50.3 (CH₂), 30.7 (2CH₃); 21.5 (CH₃), 21.3 (CH₃). **ESI-MS** calculated for C₂₂H₂₅NNaO₂S [M+Na]⁺ 390.15, found 390.21.

(E)-N-(3-(2-methoxyphenyl)allyl)-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (1d)



Product **1d** was isolated following **GP-5** as a white solid (26 %, 196 mg, 0.5 mmol) using **3a** (475 mg, 2.0 mmol) and (E)-3-(2-methoxyphenyl)prop-2-en-1-ol (361 mg, 2.2 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.77 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 7.6, 1.7 Hz, 1H), 7.25-7.20 (m, 3H), 6.95-6.86 (m, 3H), 6.37 (dt, J = 16.1, 6.4 Hz, 1H), 4.35 (dd, J = 6.4, 1.4 Hz, 2H), 3.84 (s, 3H), 2.40 (s, 3H), 2.36 (s, 1H), 1.72 (s, 6H). All the data spectra are reported in literature³⁵.

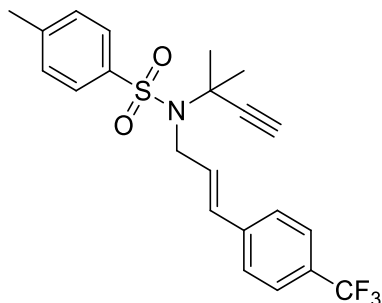
(E)-N-(3-(4-methoxyphenyl)allyl)-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (1e)



Product **1e** was isolated following **GP-3** as a white solid (27 %, 63 mg, 0.16 mmol) using **3a** (141 mg, 0.60 mmol) and (E)-1-(3-chloroprop-1-en-1-yl)-4-methoxybenzene (217 mg, 1.2 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 15.9 Hz, 1H), 6.24 (dt, J = 15.9, 6.4 Hz, 1H), 4.32 (dd, J = 6.4, 1.4 Hz, 2H), 3.81 (s, 3H), 2.39 (s, 3H), 2.37 (s, 1H), 1.71 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 159.3 (Cq), 142.9 (Cq), 139.9 (Cq), 132.0 (CH), 129.6 (Cq), 129.4 (2CH), 127.6 (2CH), 127.3 (2CH), 125.7 (CH), 114.0 (2CH), 86.5 (Cq), 72.0 (CH), 56.4 (Cq), 55.3

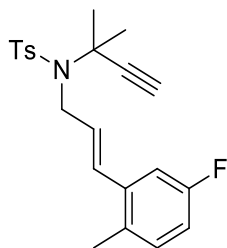
(CH₃), 50.3 (CH₂), 30.7 (2CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₂H₂₅NNKO₃S [M+K]⁺ 406.12, found 406.05.

(E)-4-methyl-N-(2-methylbut-3-yn-2-yl)-N-(3-(4-(trifluoromethyl)phenyl)allyl)benzenesulfonamide (1f)



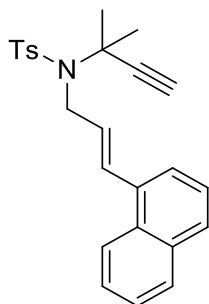
Product **1f** was isolated following **GP-5** as a white solid (22 %, 160 mg, 0.38 mmol) using **3a** (409 mg, 1.7 mmol) and (E)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (420 mg, 2.1 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.74 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.27-7.23 (m, 2H), 6.60 (d, J = 16.0 Hz, 1H), 6.47 (dt, J = 16.0, 6.0 Hz, 1H), 4.37 (dd, J = 6.1, 1.3 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 1H), 1.71 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.1 (Cq), 140.2 (Cq), 139.7 (Cq), 131.0 (CH), 130.8 (CH), 129.4 (2CH), 129.5 (q, J_{CF} = 32.4 Hz, Cq), 128.3 (CH), 127.3 (2CH), 126.6 (CH), 125.5 (q, J_{CF} = 4.0 Hz, 2CH), 124.1 (q, J_{CF} = 271.3 Hz, Cq), 86.3 (Cq), 72.2 (CH), 56.6 (Cq), 50.1 (CH₂), 30.6 (2CH₃), 21.5 (CH₃). **¹⁹F NMR** (565 MHz, CDCl₃) δ = -62.4 (s). **ESI-MS** calculated for C₂₂H₂₃F₃NO₂S [M+H]⁺ 422.14, found 422.26.

(E)-N-(3-(5-fluoro-2-methylphenyl)allyl)-4-methyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (1g)



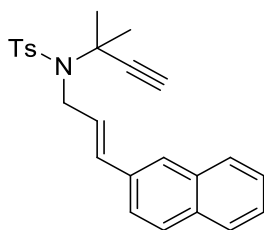
Product **1g** was isolated following **GP-5** as a white solid (32 %, 195 mg, 0.50 mmol) using **3a** (369 mg, 1.5 mmol) and (E)-3-(5-fluoro-2-methylphenyl)prop-2-en-1-ol (284 mg, 1.7 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.4 Hz, 2H), 7.27-7.25 (m, 2H), 7.10-7.06 (m, 2H), 6.85 (td, J = 8.3, 2.7 Hz, 1H), 6.75 (d, J = 15.8, 1.6 Hz, 1H), 6.22 (dt, J = 15.7, 6.2 Hz, 1H), 4.36 (dd, J = 6.3, 1.5 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 1H), 2.28 (s, 3H), 1.72 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 161.4 (d, J_{C-F} = 242.7 Hz, Cq), 143.1 (Cq), 139.8 (Cq), 137.6 (d, J_{C-F} = 7.5 Hz, Cq), 131.4 (d, J_{C-F} = 7.8 Hz, CH), 131.0 (d, J_{C-F} = 3.1 Hz, Cq), 130.2 (CH), 129.7 (CH), 129.4 (2CH), 127.3 (2CH), 114.1 (d, J_{C-F} = 21.1 Hz, CH), 112.1 (d, J_{C-F} = 21.8 Hz, CH), 86.5 (Cq), 72.2 (CH), 56.6 (Cq), 50.1 (CH₂), 30.6 (2CH₃), 21.5 (CH₃), 19.0 (CH₃). **¹⁹F NMR** (565 MHz, CDCl₃) δ = -117.6 (q, J = 8.3Hz). **ESI-MS** calculated for C₂₂H₂₄FNNaO₂S [M+Na]⁺ 408.14, found 408.16.

(E)-4-methyl-N-(2-methylbut-3-yn-2-yl)-N-(3-(naphthalen-1-yl)allyl)benzenesulfonamide
(1h)



Product **1h** was isolated following **GP-4** as a pale yellow solid (59 %, 118 mg, 0.26 mmol) using **3a** (90 mg, 0.45 mmol) and **4b** (182 mg, 0.90 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.09-8.07 (m, 1H), 7.87-7.85 (m, 1H), 7.80 (d, J = 8.3 Hz, 3H), 7.58 (d, J = 7.1 Hz, 1H), 7.52-7.44 (m, 3H), 7.36 (d, J = 15.6 Hz, 1H), 7.24 (s, 1H), 6.41 (dt, J = 15.7, 6.3 Hz, 1H), 4.47 (dd, J = 6.3, 1.5 Hz, 2H), 2.42 (s, 1H), 2.38 (s, 3H), 1.77 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.0 (Cq), 139.9 (Cq), 134.6 (Cq), 133.6 (Cq), 131.2 (Cq), 130.9 (CH), 130.1 (CH), 129.4 (2CH), 128.5 (CH), 128.0 (CH), 127.3 (2CH), 126.1 (CH), 125.8 (CH), 125.6 (CH), 124.0 (CH), 123.8 (CH), 86.6 (Cq), 72.2 (CH), 56.6 (Cq), 50.3 (CH₂), 30.7 (2CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₅H₂₅NKO₂S [M+K]⁺ 442.12, found 442.09.

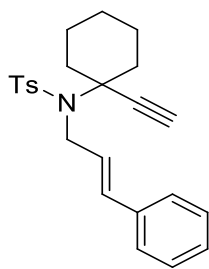
(E)-4-methyl-N-(2-methylbut-3-yn-2-yl)-N-(3-(naphthalen-2-yl)allyl)benzenesulfonamide
(1i)



Product **1i** was isolated following **GP-4** as a pale yellow solid (93 %, 139 mg, 0.28 mmol) using **3a** (71 mg, 0.3 mmol) and **4a** (122 mg, 0.6 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.82-7.77 (m, 6H), 7.72 (s, 1H), 7.60 (dd, J = 8.6, 1.8 Hz, 1H), 7.49-7.42 (m, 2H), 7.24 (s, 1H), 6.73 (d, J = 15.9 Hz, 1H), 6.50 (dt, J = 15.9, 6.3 Hz, 1H), 4.40 (dd, J = 6.3, 1.4 Hz, 2H),

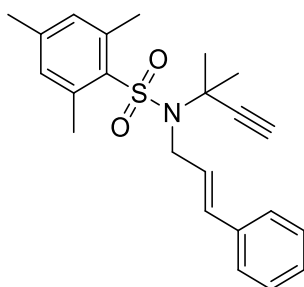
2.39 (m, 4H), 1.74 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.0 (Cq), 139.8 (Cq), 134.2 (Cq), 133.6 (Cq), 133.0 (Cq), 132.6 (CH), 129.4 (2CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.3 (2CH), 126.4 (CH), 126.3 (CH), 125.9 (CH), 86.5 (Cq), 72.1 (CH), 56.6 (Cq), 50.3 (CH₂), 30.7 (2CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₅H₂₅NNaO₂S [M+Na]⁺ 426.15, found 426.39.

N-cinnamyl-N-(1-ethynylcyclohexyl)-4-methylbenzenesulfonamide (**1l**)



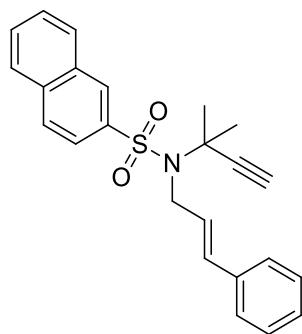
Product **1l** was isolated following **GP-3** as a pale yellow solid (73 %, 460 mg, 1.17 mmol) using **3e** (445 mg, 1.6 mmol) and (E)-(3-chloroprop-1-en-1-yl)benzene (490 mg, 3.2 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.3 Hz, 2H), 7.40-7.37 (m, 3H), 7.32 (t, J = 7.7 Hz, 2H), 7.26-7.24 (m, 2H), 6.56 (d, J = 15.9 Hz, 1H), 6.39 (dt, J = 16.0, 6.2 Hz, 1H), 4.36 (d, J = 4.7 Hz, 2H), 2.42 (s, 1H), 2.40 (s, 3H), 2.17-2.10 (m, 2H), 1.97 (td, J = 12.3, 4.2 Hz, 2H), 1.69-1.53 (m, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 142.9 (Cq), 140.0 (Cq), 136.8 (Cq), 131.9 (CH), 129.3 (2CH), 128.6 (2CH), 128.5 (CH), 127.6 (CH), 127.3 (2CH), 126.5 (2CH), 83.8 (Cq), 75.3 (CH), 62.3 (Cq), 49.8 (CH₂), 37.6 (2CH₂), 24.7 (CH₂), 23.6 (2CH₂), 21.5 (CH₃). **ESI-MS** calculated for C₂₄H₂₇NNaO₂S [M+Na]⁺ 416.17, found 416.24.

N-cinnamyl-2,4,6-trimethyl-N-(2-methylbut-3-yn-2-yl)benzenesulfonamide (**1m**)



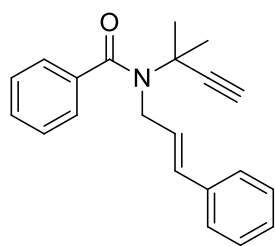
Product **1m** was isolated following **GP-3** as a white solid (71 %, 402 mg, 1.0 mmol) using **3g** (300 mg, 1.5 mmol) and (E)-(3-chloroprop-1-en-1-yl)benzene (455 mg, 3.0 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.30 (d, J = 4.3 Hz, 4H), 7.24-7.21 (m, 1H), 6.91 (s, 2H), 6.34-6.31 (m, 2H), 4.33 (d, J = 5.1 Hz, 2H), 2.65 (s, 6H), 2.44 (s, 1H), 2.25 (s, 3H), 1.69 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 142.2 (Cq), 139.3 (2Cq), 137.2 (Cq), 136.8 (Cq), 132.1 (2CH), 131.9 (CH), 128.5 (2CH), 128.1 (CH), 127.5 (CH), 126.4 (2CH), 86.8 (Cq), 72.1 (CH), 56.9 (Cq), 50.1 (CH₂), 30.1 (2CH₃); 22.9 (2CH₃), 20.9 (CH₃). **ESI-MS** calculated for C₂₃H₂₇NNaO₂S [M+Na]⁺ 404.17, found 404.20

N-cinnamyl-N-(2-methylbut-3-yn-2-yl)naphthalene-2-sulfonamide (1n)



Product **1n** was isolated following **GP-3** as a white solid (96 %, 411 mg, 1.0 mmol) using **3h** (300 mg, 1.1 mmol) and (E)-(3-chloroprop-1-en-1-yl)benzene (609 mg, 4.4 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.44 (s, 1H), 7.92-7.85 (m, 4H), 7.64-7.55 (m, 2H), 7.39-7.36 (m, 2H), 7.34-7.30 (m, 2H), 7.27-7.25 (m, 1H), 6.61 (d, J = 16.0 Hz, 1H), 6.42 (dt, J = 16.0, 6.3 Hz, 1H), 4.43 (dd, J = 6.3, 1.4 Hz, 2H), 2.35 (s, 1H), 1.75 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 139.7 (Cq), 136.7 (Cq), 134.6 (Cq), 132.7 (CH), 132.1 (Cq), 129.2 (CH), 129.0 (CH), 128.6 (3CH), 128.5 (CH), 127.8 (2CH), 127.7 (CH), 127.3 (CH), 126.5 (2CH), 122.8 (CH), 86.5 (Cq), 72.2 (CH), 56.7 (Cq), 50.3 (CH₂); 30.7 (2CH₃). **ESI-MS** calculated for C₂₄H₂₃NNaO₂S [M+Na]⁺ 412.13, found 412.53.

N-cinnamyl-N-(2-methylbut-3-yn-2-yl)benzamide (**1o**)

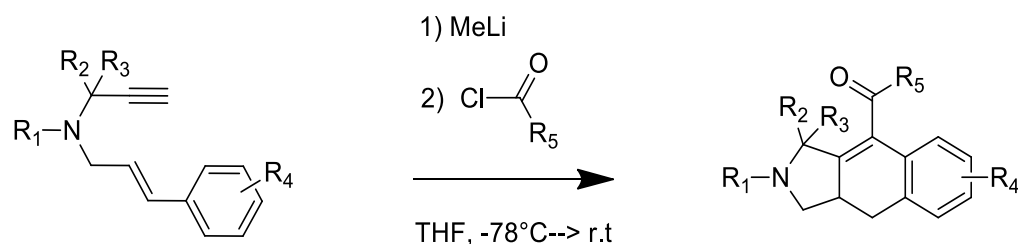


1o

In a schlenk tube a a solution of **3j** (0.80mmol, 1 equiv.) was added dropwise to a cooled suspension of sodium hydride (dispersion in mineral oil 60%) in DMF (0.61M). The mixture was stirred at 0°C for 1 hour. Then 3-bromo-1-phenyl-1-propene (1.2 mmol, 1.5 equiv.) was added to the mixture dropwise. The mixture warmed up to room temperature and stirred overnight until complete conversion. Finally saturated aqueous solution of NH₄Cl (10 ml) was added at 0°C. The resulting mixture was extracted with ethyl acetate and dried over anhydrous sodium sulfate. The solution then was concentrated under reduced pressure and purified by flash chromatography (isocratic n-Hexane/EtOAc 8:2-7:3) to afford the desired product.

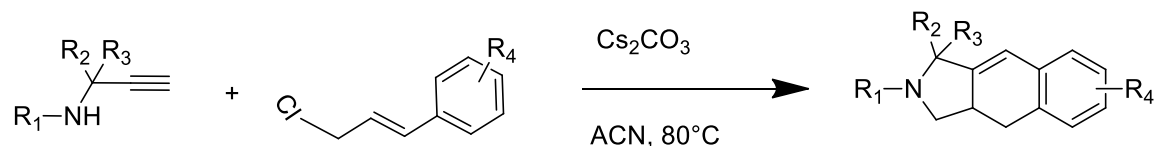
Product **1o** was isolated as a white solid (54 %, 130 mg, 0.43 mmol) using **3** (150 mg, 0.80 mmol) and 3-bromo-1-phenyl-1-propene (236 mg, 1.2 mmol) as reagents (eluent: hexane:EtOAc = 8:2-7:3). **¹H NMR** (400 MHz, CDCl₃) δ = 7.43-7.40 (m, 2H), 7.38-7.36 (m, 3H), 7.32-7.31 (m, 4H), 7.26 (s, 1H), 7.27-7.25 (m, 1H), 6.28 (d, J = 16.0 Hz, 1H), 6.16 (dt, J = 15.9, 5.6 Hz, 1H), 4.27 (dd, J = 5.7, 1.5 Hz, 2H), 2.53 (s, 1H), 1.93 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ = 172.9 (Cq, C=O), 138.3 (Cq), 136.6 (Cq), 132.1 (CH), 129.4 (CH), 128.6 (2CH), 128.3 (2CH), 127.7 (CH), 127.2 (CH), 126.6 (2CH), 126.3 (2CH), 87.7 (Cq), 72.3 (CH), 55.2 (Cq), 51.2 (CH₂), 28.6 (2CH₃). **ESI-MS** calculated for C₂₁H₂₁NNaO [M+Na]⁺ 326.15, found 326.20.

General procedure for the synthesis of dihydronaphthalenes (GP-6)



In a schlenk tube a solution of the enyne (typically 0.3 mmol, 1 equiv.) in THF (4.63 ml) was prepared. The solution was cooled to -78°C . Then a solution of MeLi (3.1 M in diethoxyethane, 1.2 equiv., previously titrated with a solution of iodine in THF 0.13 M,) was dropped slowly to the mixture (The solution of MeLi must not be too cold, It is importante to cool the solution for 15-30 minutes before its use). The resulting mixture was stirred for approximately 1 hour at -78°C . Afterwards a solution of chloroformate (typically, 0,75 mmol, 2.5 equiv.) was added to the reaction and the mixture was stirred overnight at room temperature. The reaction was quenched with a saturated solution of NH_4Cl and the organic layer was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. The desired product was isolated by flash chromatography (hexane: ethyla acetate 8:2).

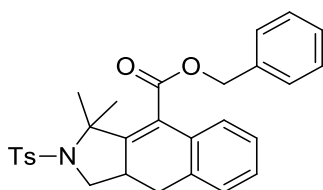
General procedure for the synthesis of dihydronaphthalenes (GP-7)



In a schlenk tube a solution of propargilamide (typically, 0.3 mmol, 1 equiv.) in acetonitrile (0.1 M) was prepared. Then Cs_2CO_3 (typically, 1.2 mmol, 4 equiv., previously put to dry at 90°C for 3-4 hours) was added to the solution. Finally a solution of Chloride (typically, 0.6 mmol, 2 equiv.) was syringed to the resulting mixture. The reaction was refluxed and monitored by TLC until completion. Once finished, the organic layer was extracted with ethyl acetate, washed with brine and dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure and the desired product was isolated by flash chromatography (Hexane: Ethyl acetate 8:2).

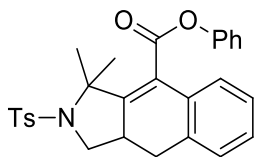
Characterization of products

Benzyl 3,3-dimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2a)



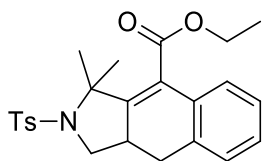
Product **2a** was isolated following **GP-6** as a white solid (82 %, 120 mg, 0.25 mmol) using **1a** (106 mg, 0.3 mmol) and a benzyl carbonochloridate (128 mg, 0.75 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.73 (d, J = 8.3 Hz, 2H), 7.42-7.35 (m, 5H), 7.28 (d, J = 8.1 Hz, 2H), 7.16-7.08 (m, 3H), 6.86-6.84 (m, 1H), 5.32 (s, 2H), 3.87-3.81 (m, 1H), 3.07-3.01 (m, 2H), 2.82 (dd, J = 15.1, 5.9 Hz, 1H), 2.62-2.54 (m, 1H), 2.41 (s, 3H), 1.76 (s, 3H), 1.57 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 168.0 (C=O), 149.5 (Cq), 143.1 (Cq), 138.0 (Cq), 134.8 (Cq), 133.0 (Cq), 132.0 (Cq), 129.5 (2CH), 129.1 (2CH), 128.7 (3CH), 127.9 (CH), 127.8 (CH), 127.3 (2CH), 127.1 (CH), 124.5 (Cq), 124.4 (CH), 68.6 (Cq), 61.4 (CH₂), 52.7 (CH₂), 37.1 (CH), 32.0 (CH₂), 28.6 (CH₃), 24.9 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₉H₂₉NNaO₄S [M+Na]⁺ 510.17, found 510.16.

Phenyl 3,3-dimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (**2b**)



Product **2b** was isolated following **GP-6** as a white solid (81 %, 116 mg, 0.24 mmol) using **1a** (106 mg, 0.3 mmol) and phenyl carbonochloridate (119 mg, 0.75 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.77 (d, J = 8.4 Hz, 2H), 7.47-7.43 (m, 2H), 7.32-7.27 (m, 2H), 7.24-7.16 (m, 6H), 3.93 (s, 1H), 3.16-3.09 (brs, 2H), 2.90 (dd, J = 15.2, 5.9 Hz, 1H), 2.71-2.63 (m, 1H), 2.42 (s, 3H), 1.90 (s, 3H), 1.82 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 166.5 (C=O), 150.8 (Cq), 150.2 (Cq), 143.2 (Cq), 138.0 (Cq), 133.1 (Cq), 131.9 (CH), 129.7 (2CH), 129.6 (2CH), 128.1 (CH), 128.0 (CH), 127.4 (2CH), 127.3 (CH), 126.4 (CH), 124.4 (CH), 124.1 (Cq), 121.3 (CH), 68.7 (Cq), 52.8 (CH₂), 37.3 (CH), 32.1 (CH₂), 28.8 (CH₃), 25.1 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₈H₂₇NNaO₄S [M+Na]⁺ 496.19, found 496.18.

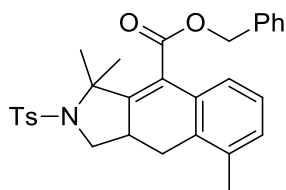
Ethyl 3,3-dimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (**2c**)



Product **2c** was isolated following **GP-6** as a brown solid (79 %, 100 mg, 0.24 mmol) using **1a** (106 mg, 0.3 mmol) and ethyl carbonochloridate (81 mg, 0.75 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.18-7.15 (m, 2H), 7.14-7.10 (m, 1H), 6.97-6.95 (m, 1H), 4.36 (qd, J = 7.1, 2.2 Hz, 2H), 3.90-3.87 (s, 1H), 3.08-3.03 (m, 2H), 2.86-2.81 (m, 1H), 2.63-2.56 (m, 1H), 2.42 (s, 3H), 1.82 (s, 3H), 1.66 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 168.2 (C=O), 149.1 (Cq), 143.1 (Cq), 138.0 (Cq), 133.1 (Cq), 132.1 (Cq), 129.5 (2CH), 127.9 (CH), 127.8 (CH), 127.3 (2CH), 127.1 (CH), 124.8 (Cq), 124.3 (CH), 68.5 (Cq), 61.4 (CH₂), 52.8 (CH₂), 37.1 (CH), 32.1 (CH₂), 28.7 (CH₃), 25.0 (CH₃), 21.5 (CH₃), 14.1 (CH₃). **ESI-MS** calculated for C₂₄H₂₇NNaO₄S [M+Na]⁺ 448.16, found 448.21.

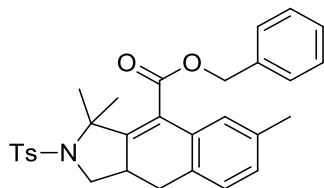
Benzyl 3,3,8-trimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate

(2d)



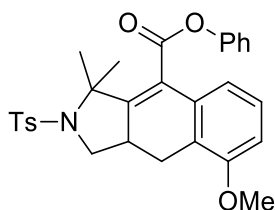
Product **2d** was isolated following **GP-6** as a white solid (78 %, 117 mg, 0.23 mmol) using **1b** (110 mg, 0.3 mmol) and benzyl carbonochloridate (128 mg, 0.75 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.3 Hz, 2H), 7.42-7.34 (m, 5H), 7.28 (d, J = 8.0 Hz, 2H), 7.04-7.01 (m, 2H), 6.73 (dd, J = 6.6, 2.4 Hz, 1H), 5.31 (s, 2H), 3.88 (m, 1H), 3.90-3.86 (m, 1H), 3.10-2.95 (m, 3H), 2.42 (s, 3H), 2.28-2.25 (m, 4H), 1.78 (s, 3H), 1.58 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 168.3 (C=O), 148.7 (Cq), 143.1 (Cq), 138.0 (Cq), 135.2 (Cq), 134.8 (Cq), 131.9 (Cq), 131.3 (Cq), 130.0 (CH), 129.5 (2CH), 129.1 (2CH), 128.7 (CH), 128.6 (2CH), 127.3 (2CH), 126.4 (CH), 124.8 (Cq), 122.5 (CH), 68.6 (Cq), 67.3 (CH₂), 53.0 (CH₂), 36.8 (CH), 28.7 (CH₂), 28.0 (CH₃), 24.9 (CH₃), 21.5 (CH₃), 19.7 (CH₃). **ESI-MS** calculated for C₃₀H₃₁NNaO₄S [M+Na]⁺ 524.19, found 524.20.

Benzyl 3,3,6-trimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate
(2e)



Product **2e** was isolated following **GP-6** as a white solid (91 %, 136 mg, 0.27 mmol) using **1c** (110 mg, 0.3 mmol) and benzyl carbonochloridate (128, 0.75 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.73 (d, J = 8.3 Hz, 2H), 7.44-7.35 (m, 5H), 7.28 (d, J = 8.3 Hz, 2H), 6.98-6.92 (m, 2H), 6.56 (s, 1H), 5.37 (d, J = 11.9 Hz, 1H), 5.29 (d, J = 11.9 Hz, 1H), 3.88-3.84 (m, 1H), 3.05-2.98 (brs, 2H), 2.78 (dd, J = 14.9, 5.8 Hz, 1H), 2.55-2.48 (m, 1H), 2.41 (s, 3H), 2.15 (s, 3H), 1.76 (s, 3H), 1.58 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 168.1 (C=O), 149.3 (Cq), 143.1 (Cq), 138.0 (Cq), 136.6 (Cq), 134.9 (Cq), 131.9 (Cq), 129.9 (CH), 129.5 (2CH), 129.3 (2CH), 128.7 (3CH), 128.4 (Cq), 127.5 (CH), 127.3 (CH), 125.1 (CH), 124.4 (Cq), 68.5 (Cq), 67.2 (CH₂), 52.8 (CH₂), 37.3 (CH), 31.6 (CH₂), 28.7 (CH₃), 24.9 (CH₃), 21.5 (CH₃), 21.0 (CH₃). **ESI-MS** calculated for C₃₀H₃₁NNaO₄S [M+Na]⁺ 524.19, found 524.20.

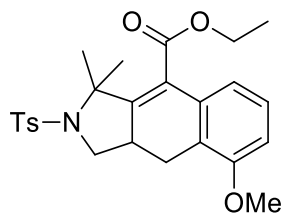
Phenyl 8-methoxy-3,3-dimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2f)



Product **2f** was isolated following **GP-6** as a white solid (71 %, 101 mg, 0.20 mmol) using **1d** (108 mg, 0.28 mmol) and phenyl carbonochloridate (111 mg, 0.71 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.77 (d, J = 8.3 Hz, 2H), 7.46-7.42 (m, 2H), 7.30 (d, J = 7.4 Hz, 3H), 7.21-7.18 (m, 3H), 6.84 (dd, J = 8.1, 2.3 Hz, 2H), 3.94 (t, J = 3.9 Hz, 1H), 3.84 (s, 3H), 3.37 (dd, J = 15.7, 6.9 Hz, 1H), 3.16-3.12 (m, 1H), 3.08-2.98 (m, 1H), 2.42 (s, 3H), 2.20 (t, J = 15.5 Hz, 1H), 1.90 (s, 3H), 1.81 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 166.6 (C=O), 156.2 (Cq), 150.9 (Cq), 150.2 (Cq), 143.2 (2Cq), 138.0 (Cq), 132.9 (Cq), 129.7 (2CH), 129.5 (2CH), 127.5 (CH), 127.3 (2CH), 126.3 (CH),

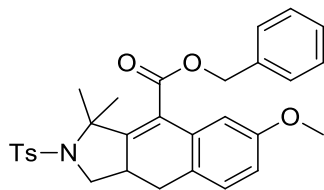
123.9 (Cq), 121.3 (2CH), 121.2 (CH), 117.1 (CH), 110.6 (CH), 68.7 (Cq), 55.6 (CH₃), 53.0 (CH₂), 36.9 (CH), 28.8 (CH₂), 25.1 (CH₃), 24.1 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₉H₂₉NNaO₅S [M+Na]⁺ 526.17, found 526.18.

Ethyl 8-methoxy-3,3-dimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2g)



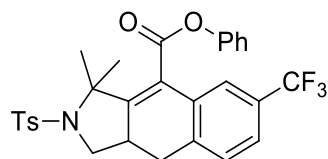
Product **2g** was isolated following **GP-6** as a white solid (65 %, 61 mg, 0.13 mmol) using **1d** (78 mg, 0.20 mmol) and ethyl carbonochloridate (56 mg, 0.51 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 7.8, 1H), 4.35 (qd, 7.2, 2.0 Hz, 2H), 3.89 (m, 1H), 3.81 (s, 3H), 3.31 (dd, *J* = 15.7, 6.9 Hz, 1H), 3.07 (dd, 10.4, 9.1 Hz, 1H), 3.01-2.91 (m, 1H), 2.41 (s, 3H), 2.13 (t, *J* = 15.2 Hz, 1H), 1.81 (s, 3H), 1.65 (s, 3H), 1.35 (t, 7.2 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 168.3 (C=O), 156.1 (Cq), 149.2 (Cq), 143.1 (Cq), 138.1 (Cq), 133.1 (Cq), 129.5 (2CH), 127.3 (2CH + Cq), 124.7 (Cq), 121.2 (CH), 117.0 (CH), 110.4 (CH), 68.6 (Cq), 61.3 (CH₂), 55.6 (CH₃), 53.0 (CH₂), 36.6 (CH), 28.7 (CH₂), 24.9 (CH₃), 24.1 (CH₃), 21.5 (CH₃), 14.1 (CH₃). **ESI-MS** calculated for C₂₅H₂₉NNaO₅S [M+Na]⁺ 478.17, found 478.53.

Benzyl 6-methoxy-3,3-dimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[*f*]isoindole-4-carboxylate (2h)



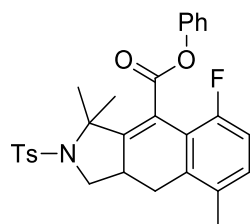
Product **2h** was isolated following **GP-6** as a white solid (74 %, 58 mg, 0.12 mmol) using **1e** (57 mg, 0.15 mmol) and benzyl carbonochloridate (64, 0.37 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.73 (d, J = 8.3 Hz, 2H), 7.44-7.42 (m, 2H), 7.39-7.33 (m, 3H), 7.28 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 7.3 Hz, 1H), 6.67 (dd, 8.2, 2.6 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 5.32 (d, J = 3.0 Hz, 2H), 3.87-3.80 (m, 1H), 3.57 (s, 3H), 3.06-2.98 (m, 2H), 2.77 (dd, J = 14.9, 5.5 Hz, 1H), 2.53-2.45 (m, 1H), 2.41 (s, 3H), 1.76 (s, 3H), 1.58 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 167.9 (C=O), 158.7 (Cq), 150.1 (Cq), 143.2 (Cq), 138.0 (Cq), 134.9 (Cq), 132.9 (Cq), 129.5 (2CH), 129.3 (2CH), 128.8 (CH), 128.7 (2CH), 128.5 (CH), 127.3 (2CH), 125.1 (Cq), 124.5 (Cq), 113.2 (CH), 110.3 (CH), 68.6 (Cq), 67.2 (CH₂), 55.2 (CH₂), 52.7 (CH₃), 37.6 (CH), 31.2 (CH₂), 28.6 (CH₃), 24.9 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₃₀H₃₁NNaO₅S [M+Na]⁺ 540.18, found 540.19.

Phenyl 3,3-dimethyl-2-tosyl-6-(trifluoromethyl)-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2i)



Product **2i** was isolated following **GP-6** as a white solid (41 %, 58 mg, 0.11 mmol) using **1f** (108 mg, 0.26 mmol) and phenyl carbonochloridate (101 mg, 0.64 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.78 (d, J = 8.3 Hz, 2H), 7.48-7.45 (m, 4H), 7.33-7.28 (m, 4H), 7.17 (d, J = 7.2 Hz, 2H), 3.96-3.93 (m, 1H), 3.17-3.12 (m, 2H), 3.01-2.95 (m, 1H), 2.70 (t, J = 14.7 Hz, 1H), 2.43 (s, 3H), 1.92 (s, 3H), 1.84 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 165.9 (C=O), 153.1 (Cq), 150.0 (Cq), 143.4 (Cq), 137.8 (Cq), 137.1 (q, J_{CF} = 1.3 Hz, Cq), 132.7 (Cq), 129.9 (2CH), 129.8 (q, J_{CF} = 32.5 Hz, Cq), 129.6 (2CH), 128.3 (CH), 127.4 (2CH), 126.6 (CH), 124.8 (q, J_{CF} = 3.7 Hz, CH), 123.3 (Cq), 123.9 (q, J_{CF} = 272.3 Hz, Cq), 121.3 (q, J_{CF} = 3.8 Hz, CH), 121.2 (2CH), 68.7 (Cq), 52.6 (CH₂), 37.1 (CH), 31.8 (CH₂), 28.8 (CH₃), 24.9 (CH₃), 21.5 (CH₃). **¹⁹F NMR** (565 MHz, CDCl₃) δ = -62.6 (s). **ESI-MS** calculated for C₂₉H₂₇F₃NO₄S [M+H]⁺ 542.16, found 542.54.

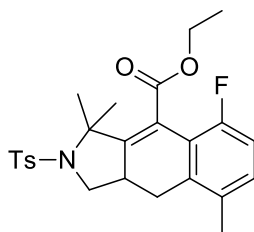
Phenyl 5-fluoro-8-methoxy-3,3-dimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2j)



Product **2j** was isolated following **GP-6** as a white solid (69 %, 91 mg, 0.18 mmol) using **1g** (100 mg, 0.26 mmol) and phenyl carbonochloridate (102 mg, 0.65 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.78 (d, J = 8.3 Hz, 2H), 7.43-7.39 (m, 2H), 7.31-7.27 (m, 3H), 7.17 (d, J = 6.6 Hz, 2H), 7.06 (dd, J = 8.5, 5.4 Hz, 1H), 6.90-6.85 (m, 1H), 3.95 (dd, J = 9.2, 7.7 Hz, 1H), 3.16 (t, J = 9.3 Hz, 1H), 3.09-3.01 (m, 2H), 2.43 (s, 3H), 2.41-2.36 (m, 1H), 2.24 (s, 3H), 1.99 (s, 3H), 1.81 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 166.3 (C=O), 157.6 (d, J_{CF} = 246 Hz, C-F), 150.4

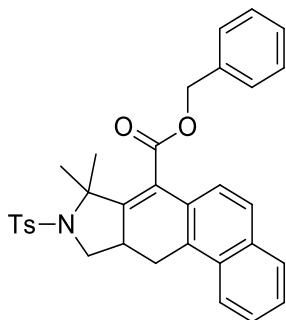
(Cq), 143.2 (2Cq), 138.0 (Cq), 134.1 (d, J_{CF} = 2.6 Hz, Cq), 131.1 (d, J_{CF} = 8.7 Hz, CH), 130.6 (d, J_{CF} = 2.9 Hz, Cq), 129.6 (4CH), 127.4 (2CH), 126.2 (CH), 121.4 (d, J_{CF} = 2.1 Hz, 2CH), 120.5 (d, J_{CF} = 11.2 Hz, Cq), 119.6 (Cq), 113.7 (d, J_{CF} = 22.4 Hz, CH), 69.4 (Cq), 52.7 (CH₂), 37.2 (CH), 29.2 (CH₂), 28.9 (d, J_{CF} = 2.6 Hz, CH₃), 24.4 (CH₃), 21.5 (CH₃), 19.3 (CH₃). **¹⁹F NMR** (565 MHz, CDCl₃) δ = -117.0 (s) **ESI-MS** calculated for C₂₉H₂₈FNKO₄S [M+K]⁺ 544.14, found 544.26.

Ethyl-5-fluoro-3,3,8-trimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2k)



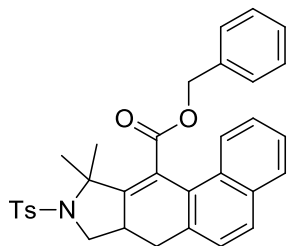
Product **2k** was isolated following **GP-6** as a white solid (68 %, 51 mg, 0.11 mmol) using **1g** (63 mg, 0.16 mmol) and ethyl carbonochloridate (44 mg, 0.41 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.00 (dd, J = 8.5, 5.3 Hz, 1H), 6.79 (m, 1H), 4.32-4.24 (m, 2H), 3.90 (dd, J = 9.1, 7.7 Hz, 1H), 3.08 (t, J = 9.3 Hz, 1H), 3.03-2.94 (m, 2H), 2.41-2.40 (m, 4H), 2.21 (s, 3H), 1.93 (s, 3H), 1.66 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 168.1 (C=O), 157.5 (d, J_{CF} = 246 Hz, C-F), 143.2 (2Cq), 138.0 (Cq), 134.0 (d, J_{CF} = 2.7 Hz, Cq), 130.8 (d, J_{CF} = 8.8 Hz, CH), 130.4 (d, J_{CF} = 3.2 Hz, Cq), 129.5 (2CH), 127.4 (2CH), 120.7 (d, J_{CF} = 11.2 Hz, Cq), 120.3 (Cq), 113.7 (d, J_{CF} = 22.7 Hz, CH), 69.3 (Cq), 61.4 (CH₂), 52.8 (CH₂), 36.8 (CH), 29.1 (CH₂), 28.9 (d, J_{CF} = 2.6 Hz, CH₃), 24.4 (CH₃), 21.5 (CH₃), 19.2 (CH₃), (13.9, CH₃). **¹⁹F NMR** (565 MHz, CDCl₃) δ = -117.8 (s) **ESI-MS** calculated for C₂₅H₂₉FNO₄S [M+H]⁺ 458.18, found 458.29.

Benzyl 8,8-dimethyl-9-tosyl-9,10,10a,11-tetrahydro-8H-naphtho[1,2-f]isoindole-7-carboxylate (2l)



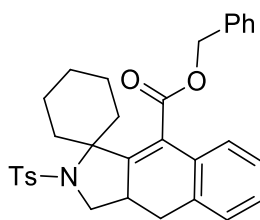
Product **2l** was isolated following **GP-6** as a white solid (53%, 68 mg, 0.13 mmol) using **1h** (97 mg, 0.24 mmol) and benzyl carbonochloridate (102 mg, 0.6 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.95 (d, J = 8.4 Hz, 1H), 7.79-7.76 (m, 3H), 7.61 (d, J = 8.6 Hz, 1H), 7.52-7.35 (m, 7H), 7.29 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.6 Hz, 1H), 5.38-5.31 (m, 2H), 3.99-3.95 (m, 1H), 3.61 (dd, J = 15.5, 6.6 Hz, 1H), 3.21-3.08 (m, 2H), 2.65 (t, J = 15.4 Hz, 1H), 2.41 (s, 3H), 1.83 (s, 3H), 1.62 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 168.2 (C=O), 149.4 (Cq), 143.2 (Cq), 138.0 (Cq), 134.8 (Cq), 133.2 (Cq), 130.9 (Cq), 129.5 (2CH), 129.3 (Cq), 129.1 (2CH), 128.7 (4CH), 128.6 (CH), 127.4 (2CH), 127.0 (CH), 126.5 (CH), 125.8 (CH), 124.9 (Cq), 123.4 (Cq), 122.6 (CH), 68.7 (Cq), 67.4 (CH₂), 53.0 (CH₂), 37.0 (CH), 28.8 (CH₂), 27.3 (CH₃), 25.0 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₃₃H₃₁NNaO₄S [M+Na]⁺ 560.19, found 560.20.

Benzyl 10,10-dimethyl-9-tosyl-7a,8,9,10-tetrahydro-7H-naphtho[1,2-f]isoindole-11-carboxylate (2m)



Product **2m** was isolated following **GP-6** as a white solid (48 %, 53 mg, 0.10 mmol) using **1i** (81 mg, 0.20 mmol) and benzyl carbonochloridate (86 mg, 0.50 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.80-7.75 (m, 4H), 7.69 (d, J = 8.2 Hz, 1H), 7.38-7.34 (m, 1H), 7.30-7.26 (m, 3H), 7.25-7.18 (m, 4H), 7.03 (d, J = 7.7, 1.7 Hz, 2H), 5.20 (d, J = 12.0 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 3.85 (t, J = 8.9 Hz, 1H), 3.16 (t, J = 9.3 Hz, 1H), 3.09-2.99 (m, 1H), 2.86 (dd, J = 15.2, 6.0 Hz, 1H), 2.71 (t, J = 15.4 Hz, 1H), 2.41 (s, 3H), 2.09 (s, 3H), 1.67 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 169.3 (C=O), 156.7 (Cq), 143.2 (Cq), 138.1 (Cq), 134.7 (Cq), 133.3 (2Cq), 130.1 (Cq), 129.8 (Cq), 129.5 (2CH), 128.8 (3CH), 128.6 (CH), 128.4 (3CH), 127.4 (2CH), 126.3 (CH), 125.7 (CH), 125.0 (CH), 123.4 (Cq), 123.3 (CH), 69.8 (Cq), 67.2 (CH₂), 52.1 (CH₂), 38.0 (CH), 34.6 (CH₂), 29.1 (CH₃), 24.2 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₃₃H₃₁NNaO₄S [M+Na]⁺ 560.19, found 560.19.

Benzyl 2-tosyl-2,3,3a,4-tetrahydrospiro[benzo[f]isoindole-1,1'-cyclohexane]-9-carboxylate (2n)

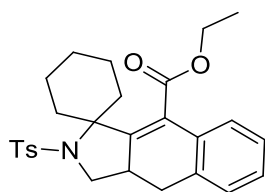


Product **2n** was isolated following **GP-6** as a white solid (43 %, 68 mg, 0.13 mmol) using **1I** (118 mg, 0.3 mmol) and benzyl carbonochloridate (128 mg, 0.75 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.73 (d, J = 8.3 Hz, 2H), 7.53-7.48 (m, 1H), 7.46-7.44 (m, 2H), 7.40-7.37 (m, 3H), 7.21 (d, J = 8.0 Hz, 2H), 7.13-7.11 (m, 1H), 7.06-7.04 (m, 1H), 7.00-6.97 (m, 1H), 5.35 (s, 2H), 3.96 (dd, J = 12.3, 8.2 Hz, 1H), 3.21 (dd, J = 12.4, 9.2 Hz, 1H), 2.82-2.75 (m, 1H), 2.67

(dd, $J = 14.7, 6.1$ Hz, 1H), 2.35 (s, 3H), 2.29 (d, $J = 15.5$ Hz, 1H), 2.22-1.71 (m, 10H). ^{13}C NMR (101 MHz, CDCl_3) $\delta = 168.5$ (C=O), 150.0 (Cq), 143.2 (Cq), 138.8 (Cq), 134.9 (Cq), 136.6 (Cq), 132.3 (Cq), 129.6 (2CH), 129.2 (2CH), 128.8 (Cq), 128.7 (3CH), 127.7 (2CH), 127.3 (2CH), 127.0 (CH), 124.1 (CH), 72.8 (Cq), 67.3 (CH_2), 52.5 (CH_2), 38.0 (CH), 35.2 (CH_2), 33.2 (CH_2), 32.3 (CH_2), 24.7 (CH_2), 22.0 (CH_2), 21.9 (CH_2), 21.5 (CH_3). **ESI-MS** calculated for $\text{C}_{32}\text{H}_{33}\text{NNaO}_4\text{S}$ $[\text{M}+\text{Na}]^+$ 550.20, found 550.22.

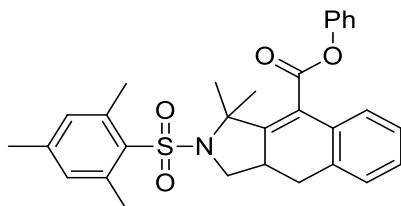
Ethyl 2-tosyl-2,3,3a,4-tetrahydrospiro[benzo[*f*]isoindole-1,1'-cyclohexane]-9-carboxylate

(2o)



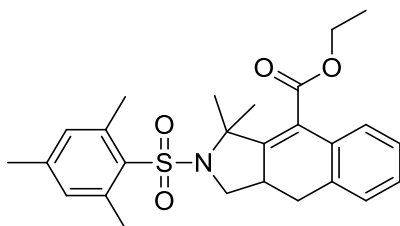
Product **2o** was isolated following **GP-6** as a white solid (26 %, 29 mg, 0.06 mmol) using **11** (93mg, 0.24 mmol) and ethyl carbonochloridate (64 mg, 0.6 mmol) as reagents (eluent: hexane:EtOAc = 8:2). ^1H NMR (400 MHz, CDCl_3) $\delta = 7.78$ (d, $J = 8.3$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.19-7.14 (m, 2H), 7.10-7.07 (m, 2H), 4.41 (qd, $J = 7.1, 1.2$ Hz, 2H), 4.02 (dd, $J = 12.3, 8.2$ Hz, 1H), 3.26 (dd, $J = 12.3, 9.3$ Hz, 1H), 2.87-2.77 (m, 1H), 2.72 (dd, $J = 14.7, 6.1$ Hz, 1H), 2.39 (s, 3H), 2.30-1.76 (m, 10H), 1.42 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) $\delta = 168.5$ (C=O), 149.6 (Cq), 143.2 (Cq), 138.9 (Cq), 133.6 (Cq), 132.3 (Cq), 129.6 (2CH), 127.7 (2CH), 127.3 (2CH), 127.1 (CH), 124.1 (CH), 72.7 (Cq), 61.4 (CH_2), 52.5 (CH_2), 37.9 (CH), 35.2 (CH_2), 33.1 (CH_2), 32.3 (CH_2), 24.9 (CH_2), 22.1 (CH_2), 22.0 (CH_2), 21.5 (CH_3), 14.2 (CH_3). **ESI-MS** calculated for $\text{C}_{27}\text{H}_{31}\text{KNO}_4\text{S}$ $[\text{M}+\text{K}]^+$ 504.16, found 504.19.

Phenyl 2-(mesitylsulfonyl)-3,3-dimethyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2p)



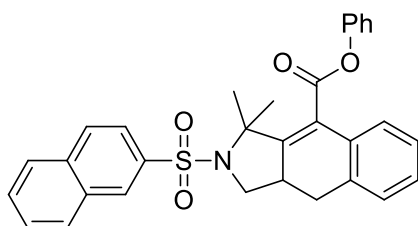
Product **2p** was isolated following **GP-6** as a white solid (73 %, 97 mg, 0.19 mmol) using **1m** (100 mg, 0.26 mmol) and phenyl carbonochloridate (103 mg, 0.66 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.48-7.44 (m, 2H), 7.32-7.28 (m, 1H), 7.26-7.15 (m, 6H), 6.96 (s, 2H), 3.42 (t, J = 8.4 Hz, 1H), 3.18 (dd, J = 10.3, 8.9 Hz, 1H), 3.06-2.96 (m, 2H), 2.84 (dd, J = 14.9, 6.2 Hz, 1H), 2.70 (s, 7H), 2.31 (s, 3H), 1.97 (s, 3H), 1.93 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 166.5 (C=O), 151.4 (Cq), 150.3 (Cq), 142.8 (Cq), 140.2 (2Cq), 134.0 (Cq), 133.4 (Cq), 132.0 (2CH), 129.7 (2CH), 128.1 (CH), 128.0 (CH), 127.3 (CH), 126.4 (CH), 124.3 (CH), 123.8 (Cq), 121.3 (2CH), 69.3 (Cq), 51.5 (CH₂), 37.4 (CH), 32.2 (CH₂), 27.8 (CH₃), 25.3 (CH₃), 22.9 (2CH₃), 21.0 (CH₃), **ESI-MS** calculated for C₃₀H₃₂NO₄S [M+H]⁺ 502.21, found 502.05.

Ethyl 2-(mesitylsulfonyl)-3,3-dimethyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2q)



Product **2q** was isolated following **GP-6** as a white solid (63 %, 76 mg, 0.17 mmol) using **1m** (102 mg, 0.27 mmol) and ethyl carbonochloridate (73 mg, 0.67 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.19-7.13 (m, 2H), 7.11-7.09 (m, 1H), 7.02 (dd, J = 7.3, 1.6 Hz, 1H), 6.94 (s, 2H), 4.39 (dd, J = 7.2, 6.2 Hz, 2H), 3.36 (dd, J = 9.0, 7.8 Hz, 1H), 3.11 (dd, J = 10.2, 8.9 Hz, 1H), 2.98-2.88 (m, 1H), 2.78 (dd, J = 14.8, 6.2 Hz, 1H), 2.70-2.63 (m, 7H), 2.30 (s, 3H), 1.83 (s, 3H), 1.82 (s, 3H), 1.39 (t, J = 1.4 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 168.2 (C=O), 149.8 (Cq), 142.7 (Cq), 140.2 (2Cq), 134.0 (Cq), 133.3 (Cq), 132.2 (Cq), 132.0 (2CH), 127.8 (2CH), 127.2 (CH), 124.6 (Cq), 124.3 (CH), 69.2 (Cq), 61.4 (CH₂), 51.5 (CH₂), 37.2 (CH), 32.2 (CH₂), 27.5 (CH₃), 25.3 (CH₃), 22.9 (2CH₃), 21.0 (CH₃), 14.2 (CH₃). **ESI-MS** calculated for C₂₆H₃₂NO₄S [M+H]⁺ 454.21, found 454.32.

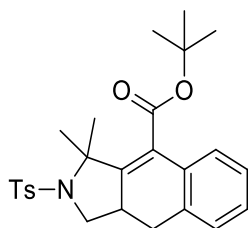
Phenyl 3,3-dimethyl-2-(naphthalen-2-ylsulfonyl)-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2r)



Product **2r** was isolated following **GP-6** as a white solid (96 %, 103 mg, 0.20 mmol) using **1n** (80 mg, 0.20 mmol) and phenyl carbonochloridate (80 mg, 0.51 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.46 (s, 1H), 8.00-7.95 (m, 2H), 7.92-7.87 (m, 2H), 7.67-7.59 (m, 2H), 7.47-7.43 (m, 2H), 7.30 (d, J = 7.5 Hz, 1H), 7.24-7.15 (m, 6H), 3.99 (dd, J = 8.7, 7.6 Hz, 1H), 3.23-3.08 (m, 2H), 2.89 (dd, J = 15.0, 6.1 Hz, 1H), 2.67 (t, J = 15.0 Hz, 1H), 1.96 (s, 3H), 1.88 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 166.5 (C=O), 150.7 (Cq), 150.2 (Cq), 137.8 (Cq), 134.7 (Cq),

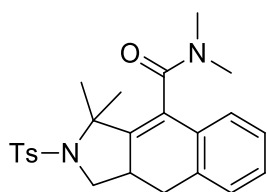
133.1 (Cq), 132.1 (Cq), 131.9 (Cq), 129.7 (2CH), 129.3 (2CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.3 (CH), 126.4 (CH), 124.4 (CH), 124.2 (Cq), 122.7 (CH), 121.3 (2CH), 68.9 (Cq), 52.9 (CH₂), 37.3 (CH), 32.0 (CH₂), 28.8 (CH₃), 25.4 (CH₃). **ESI-MS** calculated for C₃₁H₂₇NNaO₄S [M+Na]⁺ 532.16, found 532.24.

Tert-butyl 3,3-dimethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxylate (2s)



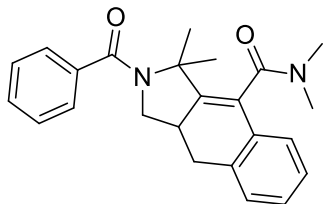
Product **2s** was isolated following **GP-6** as a white solid (34 %, 46 mg, 0.10 mmol) using **1a** (106 mg, 0.3 mmol) and di-tert-butyl dicarbonate (164 mg, 0.75 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.75 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.20-7.09 (m, 3H), 7.05 (dd, *J* = 7.0, 2.0 Hz, 1H), 3.90-3.83 (m, 1H), 3.07-3.00 (m, 2H), 2.81 (dd, *J* = 15.0, 5.5 Hz, 1H), 2.62-2.55 (m, 1H), 2.42 (s, 3H), 1.84 (s, 3H), 1.72 (s, 3H), 1.59 (s, 9H). **¹³C NMR** (101 MHz, CDCl₃) δ = 167.5 (C=O), 147.6 (Cq), 143.1 (Cq), 138.1 (Cq), 133.2 (Cq), 132.7 (Cq), 129.5 (2CH), 127.7 (CH), 127.6 (CH), 127.3 (2CH), 127.1 (CH), 125.8 (Cq), 124.1 (CH), 82.9 (Cq), 68.6 (Cq), 52.8 (CH₂), 37.0 (CH), 32.1 (CH₂), 28.6 (CH₃), 28.1 (3CH₃), 25.1 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₆H₃₁NNaO₄S [M+Na]⁺ 476.19, found 476.17.

N,N,3,3-tetramethyl-2-tosyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxamide (2t)



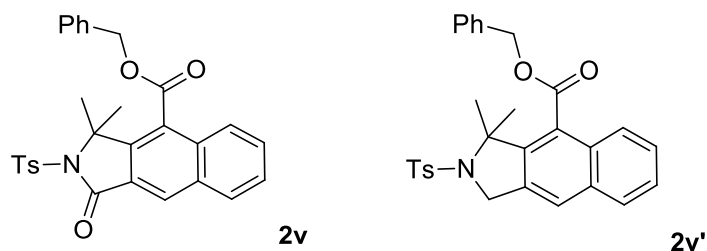
Product **2t** was isolated following **GP-6** as a white solid (64 %, 82 mg, 0.19 mmol) using **1a** (108 mg, 0.3 mmol) and dimethylcarbamic chloride (81 mg, 0.75 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.17-7.11 (m, 3H), 6.97-6.95 (m, 1H), 3.86-3.82 (m, 1H), 3.12-3.08 (m, 1H), 3.07 (s, 3H), 3.05-2.99 (m, 1H), 2.88 (dd, J = 14.9, 6.2 Hz, 1H), 2.74 (s, 3H), 2.52 (t, J = 14.8 Hz, 1H), 2.42 (s, 3H), 1.82 (s, 3H), 1.66 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 168.4 (C=O), 147.3 (Cq), 143.0 (Cq), 138.2 (Cq), 132.7 (Cq), 132.0 (Cq), 129.5 (2CH), 127.8 (2CH), 127.5 (CH), 127.3 (2CH), 126.9 (Cq), 123.9 (CH), 68.8 (Cq), 53.1 (CH₂), 38.1 (CH), 36.9 (CH₃), 34.2 (CH₃), 32.4 (CH₂), 28.9 (CH₃), 24.2 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₄H₂₉N₂O₃S [M+H]⁺ 425.19, found 425.31.

2-benzoyl-N,N,3,3-tetramethyl-2,3,9,9a-tetrahydro-1H-benzo[f]isoindole-4-carboxamide
(2u)



Product **2u** was isolated following **GP-6** as a white solid (33 %, 33 mg, 0.09 mmol) using **1o** (83 mg, 0.3 mmol) and dimethylcarbamic chloride (73 mg, 0.67 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.43-7.38 (m, 5H), 7.19-7.15 (m, 2H), 7.14-7.11 (m, 1H), 7.01-6.99 (m, 1H), 3.82 (brs, 1H), 3.27 (t, J = 10.6 Hz, 1H), 3.18-3.13 (m, 1H), 3.11 (s, 3H), 2.88-2.82 (m, 4H), 2.53 (t, J = 15.0 Hz, 1H), 1.94 (s, 3H), 1.80 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 169.2 (C=O), 168.7 (C=O), 147.7 (Cq), 138.8 (Cq), 132.6 (Cq), 132.1 (Cq), 129.3 (CH), 128.4 (2CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 126.6 (Cq), 126.2 (2CH), 123.9 (CH), 66.2 (Cq), 55.9 (CH₂), 38.2 (CH), 37.0 (CH₃), 34.2 (CH₃), 32.6 (CH₂), 26.4 (CH₃), 21.1 (CH₃). **ESI-MS** calculated for C₂₄H₂₇N₂O₂ [M+H]⁺ 375.21 found 375.28.

2-(benzyloxy)-1-(3,3-dimethyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindol-4-yl)ethanone (2v)
and 4-(2-(benzyloxy)acetyl)-3,3-dimethyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindol-1-one (2v')

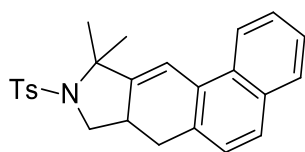


In a round bottom flask a solution of **2a** (66 mg, 0.13 mmol) in dichloromethane was prepared. Then MnO_2 (469 mg, 5.4 mmol) was added and the resulting suspension was stirred at room temperature until completion. Once finished, The solid was removed by filtration over a pad of celite and the crude was concentrated under reduced pressure. Purification by column chromatography (hexane:EtOAc = 8:2) afforded the products **5f** and **5f'**.

Product **5f** was isolated as a white solid (44 %, 29 mg, 0.06 mmol) using **2a** (66 mg, 0.13 mmol) and MnO_2 (469 mg, 5.4 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **^1H NMR** (400 MHz, CDCl_3) δ = 8.39 (s, 1H), 7.85 (d, J = 7.3 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 7.5, 1.9 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.61-7.54 (m, 2H), 7.52-7.50 (m, 2H), 7.43-7.41 (m, 3H), 7.32 (d, J = 8.2 Hz, 2H), 5.56 (s, 2H), 2.41 (s, 3H), 2.00 (s, 6H). **^{13}C NMR** (101 MHz, CDCl_3) δ = 168.0 (Cq), 165.2 (Cq), 145.0 (Cq), 142.7 (Cq), 136.6 (Cq), 134.4 (Cq), 133.2 (Cq), 132.6 (Cq), 129.9 (CH), 129.7 (CH), 129.4 (2CH), 129.3 (2CH), 129.1 (CH), 128.8 (4CH), 127.7 (CH), 127.3 (CH), 125.2 (CH), 70.4 (Cq), 68.2 (CH_2), 26.5 (2 CH_3), 21.7 (CH_3). **ESI-MS** calculated for $\text{C}_{29}\text{H}_{26}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 500.15 found 500.34.

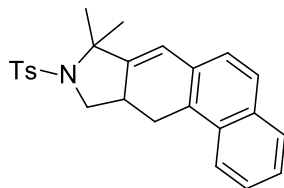
Product **5f'** was isolated as a white solid (22 %, 15 mg, 0.03 mmol) using **2a** (66 mg, 0.13 mmol) and MnO_2 (469 mg, 5.4 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **^1H NMR** (400 MHz, CDCl_3) δ = 7.80-7.75 (m, 3H), 7.67 (s, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.49-7.38 (m, 7H), 7.28 (d, J = 8.3 Hz, 2H), 5.50 (s, 2H), 4.71 (s, 2H), 2.40 (s, 3H), 1.83 (s, 6H). **^{13}C NMR** (101 MHz, CDCl_3) δ = 168.4 (Cq), 143.2 (Cq), 141.6 (Cq), 138.0 (Cq), 134.7 (Cq), 132.7 (2Cq), 129.5 (2CH), 129.2 (2CH), 128.8 (CH), 128.7 (2CH), 127.8 (CH), 127.3 (2CH), 126.9 (CH), 126.5 (Cq), 124.8 (CH), 122.8 (CH), 71.5 (Cq), 67.8 (CH_2), 51.7 (CH_2), 27.3 (2 CH_3), 21.5 (CH_3). **ESI-MS** calculated for $\text{C}_{29}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 486.17 found 486.12.

10,10-dimethyl-9-tosyl-7a,8,9,10-tetrahydro-7H-naphtho[1,2-f]isoindole (5a)



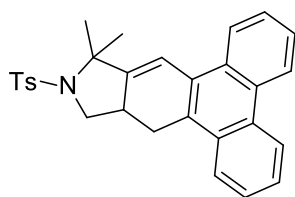
Product **5a** was isolated following **GP-7** as a pale yellow solid (93 %, 112 mg, 0.28 mmol) using **3a** (71 mg, 0.3 mmol) and **4a** (122 mg, 0.6 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.06 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.3 Hz, 3H), 7.65 (d, J = 8.4 Hz, 1H), 7.52-7.4 (m, 1H), 7.45-7.40 (m, 1H), 7.31-7.26 (m, 3H), 6.99 (d, J = 2.8 Hz, 1H), 3.95 (t, J = 8.1 Hz, 1H), 3.22-3.07 (m, 2H), 3.01 (dd, J = 15.2, 6.8 Hz, 1H), 2.73 (t, J = 15.6 Hz, 1H), 2.42 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 153.1 (Cq), 143.0 (Cq), 138.0 (Cq), 133.0 (Cq), 130.8 (Cq), 129.5 (2CH + Cq), 129.1 (Cq), 128.6 (CH), 127.4 (2CH), 127.0 (CH), 126.6 (CH), 126.1 (CH), 125.2 (CH), 122.3 (CH), 113.0 (CH), 67.6 (Cq), 53.7 (CH₂), 36.3 (CH), 33.6 (CH₂), 30.5 (CH₃), 27.3 (CH₃), 21.5 (CH₃). **ESI-MS** calculated per C₂₅H₂₆NO₂S [M+H]⁺ 404.17, found 404.26.

8,8-dimethyl-9-tosyl-9,10,10a,11-tetrahydro-8H-naphtho[1,2-f]isoindole (5b)



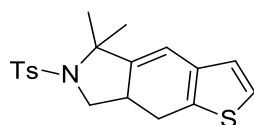
Product **5b** was isolated following **GP-7** as a pale yellow solid (81 %, 98 mg, 0.24 mmol) using **3a** (71 mg, 0.3 mmol) and **4b** (122 mg, 0.6 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.96 (d, J = 8.5 Hz, 1H), 7.81-7.76 (m, 3H), 7.68 (d, J = 8.4 Hz, 1H), 7.51-7.47 (m, 1H), 7.43-7.37 (m, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.4 Hz, 1H), 6.30 (d, J = 2.6 Hz, 1H), 4.02-3.99 (s, 1H), 3.66 (dd, J = 15.5, 7.0 Hz, 1H), 3.21-3.12 (m, 2H), 2.60 (t, J = 15.2 Hz, 1H), 2.42 (s, 3H), 1.71 (s, 3H), 1.65 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 151.6 (Cq), 143.0 (Cq), 138.0 (Cq), 133.2 (Cq), 131.3 (2Cq), 129.5 (2CH), 128.7 (CH), 128.0 (Cq), 127.4 (2CH), 127.0 (CH), 126.3 (CH), 125.4 (CH), 125.1 (CH), 123.2 (CH), 118.0 (CH), 67.3 (Cq), 54.0 (CH₂), 36.3 (CH), 30.3 (CH₂), 27.6 (CH₃), 27.1 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₅H₂₅NKO₂S [M+K]⁺ 442.12, found 442.22.

12,12-dimethyl-11-tosyl-9a,10,11,12-tetrahydro-9H-phenanthro[9,10-f]isoindole (5c)



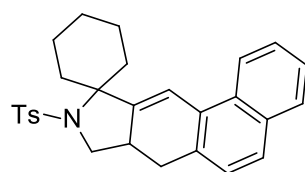
Product **5c** was isolated following **GP-7** as a white solid (77 %, 98 mg, 0.23 mmol) using **3a** (71 mg, 0.3 mmol) and **4c** (152 mg, 0.6 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.72-8.70 (m, 2H), 8.17-8.15 (m, 1H), 8.08-8.06 (m, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.65-7.60 (m, 4H), 7.32 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 2.4 Hz, 1H), 4.04 (s, 1H), 3.71 (dd, J = 15.9, 7.2 Hz, 1H), 3.24-3.17 (m, 2H), 2.67 (t, J = 15.7 Hz, 1H), 2.43 (s, 3H), 1.80 (s, 3H), 1.73 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 152.5 (Cq), 143.1 (Cq), 138.0 (Cq), 130.4 (Cq), 129.9 (Cq), 129.7 (Cq), 129.5 (2CH), 128.9 (Cq), 127.8 (Cq), 127.4 (2CH), 127.1 (Cq), 126.9 (CH), 126.8 (CH), 126.1 (CH), 126.0 (CH), 123.7 (CH), 123.1 (3CH), 113.5 (CH), 67.7 (Cq), 54.0 (CH₂), 36.0 (CH), 30.6 (CH₂), 28.9 (CH₃), 27.3 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₂₉H₂₈NO₂S [M+H]⁺ 454.18, found 454.48.

5,5-dimethyl-6-tosyl-6,7,7a,8-tetrahydro-5H-thieno[2,3-f]isoindole (5d)



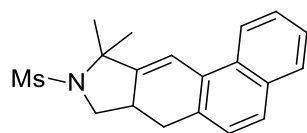
Product **5d** was isolated following **GP-7** as a brown solid (73 %, 80 mg, 0.22 mmol) using **3a** (72 mg, 0.3 mmol) and **4d** (96 mg, 0.6 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.04 (dd, J = 5.0, 1.2 Hz, 1H), 6.82 (d, J = 5.1 Hz, 1H), 6.19 (d, J = 3.1 Hz, 1H), 3.86 (t, J = 8.5 Hz, 1H), 3.27-3.18 (m, 1H), 3.07-2.99 (m, 2H), 2.58-2.50 (m, 1H), 2.41 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 148.7 (Cq), 143.0 (Cq), 138.0 (Cq), 135.1 (Cq), 132.2 (Cq), 129.5 (2CH), 127.4 (2CH), 125.1 (CH), 122.6 (CH), 112.9 (CH), 66.8 (Cq), 53.0 (CH₂), 37.8 (CH), 30.3 (CH₂), 27.5 (CH₃), 27.4 (CH₃), 21.5 (CH₃). **ESI-MS** calculated for C₁₉H₂₂NO₂S₂ [M+H]⁺ 360.11, found 360.01.

9'-tosyl-7',7a',8',9'-tetrahydrospiro[cyclohexane-1,10'-naphtho[1,2-f]isoindole] (5e)



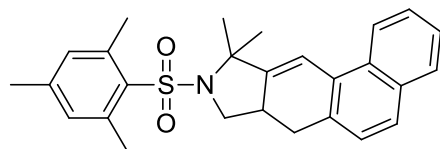
Product **5e** was isolated following **GP-7** as a white solid (40 %, 28 mg, 0.06 mmol) using **3e** (41 mg, 0.15 mmol) and **4a** (60 mg, 0.3 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.04 (d, J = 8.5 Hz, 1H), 7.80-7.78 (m, 3H), 7.65 (d, J = 8.2 Hz, 1H), 7.52 (dd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.46-7.44 (m, 2H), 7.30-7.28 (m, 3H), 3.90 (t, J = 8.4 Hz, 1H), 3.19 (dd, J = 9.9, 8.9 Hz, 1H), 3.13-3.05 (m, 1H), 2.97 (dd, J = 15.2, 6.6 Hz, 1H), 2.76 (d, J = 15.9 Hz, 1H), 2.41 (s, 3H), 2.12-1.64 (m, 10H). **¹³C NMR** (101 MHz, CDCl₃) δ = 151.0 (Cq), 142.9 (Cq), 138.9 (Cq), 133.0 (Cq), 130.7 (Cq), 129.6 (Cq), 129.5 (2CH), 129.3 (Cq), 128.7 (CH), 127.2 (2CH), 127.1 (CH), 126.5 (CH), 126.3 (CH), 125.1 (CH), 122.2 (CH), 115.5 (CH), 70.9 (Cq), 53.4 (CH₂), 36.8 (CH), 35.8 (CH₂), 35.0 (CH₂), 33.6 (CH₂), 24.5 (CH₂), 23.0 (CH₂), 21.5 (CH₃). **ESI-MS** calculated per C₂₈H₂₉NNaO₂S [M+Na]⁺ 466.18, found 466.24.

10,10-dimethyl-9-(methylsulfonyl)-7a,8,9,10-tetrahydro-7H-naphtho[1,2-f]isoindole (5f)



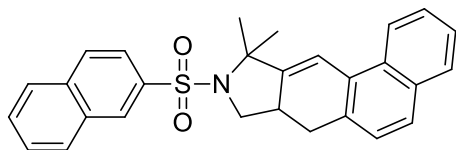
Product **5f** was isolated following **GP-7** as a white solid (60 %, 66 mg, 0.23 mmol) using **3i** (55 mg, 0.34 mmol) and **4a** (138 mg, 0.68 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.09 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 6.7 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.54-7.50 (m, 1H), 7.46-7.43 (m, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 2.9 Hz, 1H), 4.04 (t, J = 8.2 Hz, 1H), 3.31-3.18 (m, 2H), 3.09 (dd, J = 15.2, 6.8 Hz, 1H), 2.97 (s, 3H), 2.80 (t, J = 15.6 Hz, 1H), 1.77 (s, 3H), 1.71 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 152.6 (Cq), 133.1 (Cq), 130.7 (Cq), 129.5 (Cq), 129.0 (Cq), 128.6 (CH), 127.1 (CH), 126.6 (CH), 126.2 (CH), 125.2 (CH), 122.3 (CH), 113.4 (CH), 66.9 (Cq), 53.9 (CH₂), 39.9 (CH₃), 36.2 (CH), 33.7 (CH₂), 30.5 (CH₃), 27.0 (CH₃). **ESI-MS** calculated per C₁₉H₂₂NO₂S [M+H]⁺ 328.14, found 328.46.

9-(mesitylsulfonyl)-10,10-dimethyl-7a,8,9,10-tetrahydro-7H-naphtho[1,2-f]isoindole (5g)



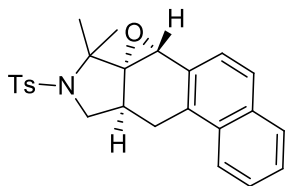
Product **5g** was isolated following **GP-7** as a white solid (92 %, 119 mg, 0.28 mmol) using **3g** (80 mg, 0.3 mmol) and **4a** (122 mg, 0.6 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.08 (d, J = 8.5 Hz, 1H), 7.79 (dd, J = 8.1, 1.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.53-7.48 (m, 1H), 7.45-7.40 (m, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 2.9 Hz, 1H), 6.96 (s, 2H), 3.42 (t, J = 8.1 Hz, 1H), 3.19-3.14 (m, 1H), 3.09-3.02 (m, 1H), 2.94 (dd, J = 15.1, 6.6 Hz, 1H), 2.81-2.75 (m, 1H), 2.71 (s, 6H), 2.31 (s, 3H), 1.86 (s, 3H), 1.80 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 153.8 (Cq), 142.7 (Cq), 140.3 (2Cq), 133.9 (Cq), 133.0 (Cq), 132.0 (2CH), 131.0 (CH), 129.5 (Cq), 129.3 (Cq), 128.6 (CH), 126.9 (CH), 126.6 (CH), 126.1 (CH), 125.2 (Cq), 122.4 (CH), 112.8 (CH), 68.2 (Cq), 52.5 (CH₂), 36.4 (CH), 33.7 (CH₂), 29.4 (CH₃), 27.7 (CH₃), 22.9 (2CH₃), 21.0 (CH₃). **ESI-MS** calculated per C₂₇H₃₀NO₂S [M+H]⁺ 432.20, found 432.05.

10,10-dimethyl-9-(naphthalen-2-ylsulfonyl)-7a,8,9,10-tetrahydro-7H-naphtho[1,2-f]isoindole (5h)



Product **5h** was isolated following **GP-7** as a white solid (89 %, 118 mg, 0.27 mmol) using **3g** (80 mg, 0.3 mmol) and **4a** (122 mg, 0.6 mmol) as reagents (eluent: hexane:EtOAc = 8:2 → 3:2). **¹H NMR** (400 MHz, CDCl₃) δ = 8.48 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 8.0-7.95 (m, 2H), 7.92-7.89 (m, 2H), 7.79 (d, J = 6.7 Hz, 1H), 7.65-7.61 (m, 3H), 7.51-7.47 (m, 1H), 7.44-7.40 (m, 1H), 7.27-7.24 (m, 1H), 7.0 (d, J = 2.3 Hz, 1H), 4.00 (s, 1H), 3.20-3.14 (m, 2H), 3.0 (dd, J = 15.4, 6.3 Hz, 1H), 2.76-2.69 (m, 1H), 1.80 (s, 3H), 1.76 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 152.9 (Cq), 137.8 (Cq), 134.7 (Cq), 133.0 (Cq), 132.2 (Cq), 130.8 (Cq), 129.5 (Cq), 129.3 (CH), 129.2 (CH), 129.1 (Cq), 128.7 (CH), 128.6 (2CH), 127.9 (CH), 127.4 (CH), 127.0 (CH), 126.6 (CH), 126.1 (CH), 125.2 (CH), 122.8 (CH), 122.3 (CH), 113.1 (CH), 67.8 (Cq), 53.8 (CH₂), 36.3 (CH), 33.6 (CH₂), 30.5 (CH₃), 27.5 (CH₃). **ESI-MS** calculated for C₂₈H₂₆NO₂S [M+H]⁺ 440.17, found 440.52.

(1aR,4aS,11bR)-2,2-dimethyl-3-tosyl-2,3,4,4a,5,11b-hexahydronaphtho[2,1-f]oxireno[2,3-d]isoindole (5i)



In a round bottom flask a solution of **5i** (52 mg, 0.13 mmol) in DCM (0.02 M) was prepared. Then the solution was cooled to 0°C and chloro perbenzoic acid (67.3 mg, 0.39 mmol) was added. Finally the resulting mixture was warmed up to room temperature and stirred until completion. Once finished, the organic layer was extracted with ethyl acetate, washed with brine and dried over Na₂SO₄. The organic layer was concentrated under reduced pressure and the desired product **5e** was isolated by flash chromatography (Hexane: Ethyl acetate 8:2).

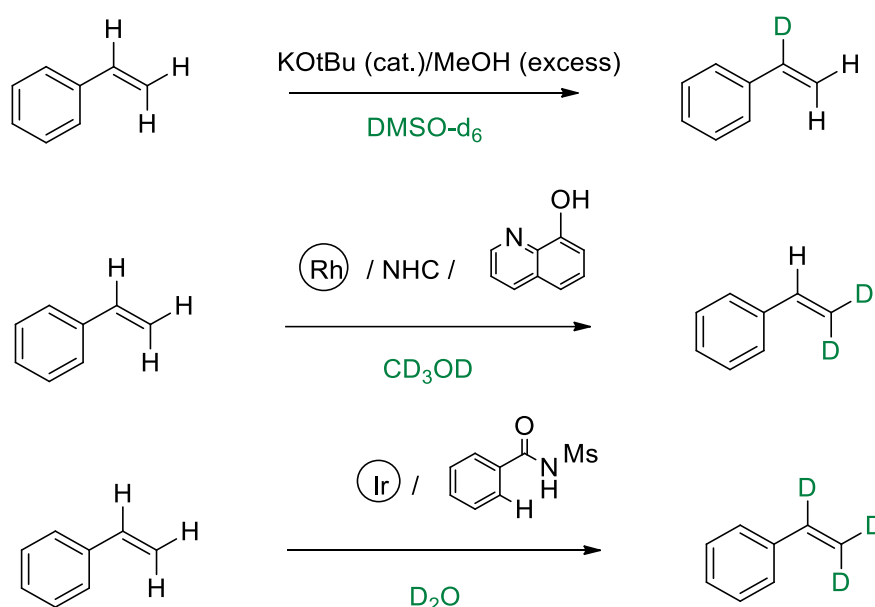
Product **5e** was isolated as a brown solid (41 %, 22.6 mg, 0.05 mmol) using **5b** (52 mg, 0.13 mmol) and a meta chloro perbenzoic acid (67.3 mg, 0.39 mmol) as reagents (eluent: hexane:EtOAc = 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.99 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.55-7.46 (m, 3H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.13-4.07 (m, 1H), 3.98 (s, 1H), 3.50-3.46 (m, 1H), 3.21 (dd, *J* = 11.0, 8.5 Hz, 1H), 2.75-2.64 (m, 2H), 2.43 (s, 3H), 1.66 (s, 3H), 1.37 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.0 (Cq), 138.2 (Cq), 133.9 (Cq), 132.4 (Cq), 131.7 (Cq), 129.8 (Cq), 129.6 (2CH), 128.8 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 126.5 (CH), 126.1 (CH), 123.2 (CH), 75.5 (Cq), 64.8 (Cq), 56.0 (CH), 51.4 (CH₂), 34.7 (CH), 28.2 (CH₂), 23.0 (CH₃), 21.5 (CH₃), 21.0 (CH₃). **ESI-MS** calculated for C₂₅H₂₅NNaO₃S [M+Na]⁺ 442.15, found 442.36.

CHAPTER 3

Functionalization of Alkenyl C–H Bonds with D_2O via Pd(0)/ Carboxylic Acid Catalysis

Introduction

The C-H functionalization which allows the conversion of simple reagents to their corresponding deuterated ones is one of most useful methods for the construction of labelled compounds.⁴⁰ These compounds can serve as tools for mechanistic studies in chemical reactions and even marketed drugs in medicine. Generally these transformations are difficult and expensive due to the strength of C-H bond⁴³ and many studies were devoted to the construction of labelled compounds. Many catalytic strategies were developed for the H/D exchange of Ar-H⁴¹ and Alk-H⁴². Moreover during the last decade particular attention was given to styrenes for studying the H/D exchange of alkenyl C(sp²)-H (Scheme 1), because they are widely used for many applications. Deuterated styrenes could be good reactants for the preparation of styryl-ynes in order to afford their corresponding naphthalenes and dihydronaphthalenes, compounds previously described in chapter 1 and 2.



Scheme 1. Catalytic deuteration of alkenyl C(sp²)-H bonds of styrenes

The preparation of deuterated styrenes can be achieved selectively at α-position through a strong alkoxide and acidic deuterium source such as dimethyl sulfoxide. (Scheme 1).^{44a} On the other hand deuteration at β C(sp²)-H can be accomplished by using Rhodium hydride with a N-heterocyclic carbene as ligand and MeOD as source of deuterium.^{44b} A similar strategy was provided employing a combination of Iridium hydride, arylsulfonamide and deuterium oxide.^{44b} We focused our attention on the *in situ* production of palladium hydrides as part of our studies in the reactivity of unsaturated substrates with palladium catalysts in the presence of carboxylic acids. This catalytic method was applied in the synthesis of tetrahydrocarbolines from their corresponding propargylated tryptamines through a peculiar C-H activation of unprotected indoles^{45d} (Figure 1). Moreover it was employed for the conversion of internal alkynes into 1,3 dienes.^{45a} (Figure 2) We discovered that this catalytic approach could be applied for the conversion of styrenes into their corresponding deuterated ones, performing the reaction in a mixture of toluene / D₂O at reflux (Figure 3).

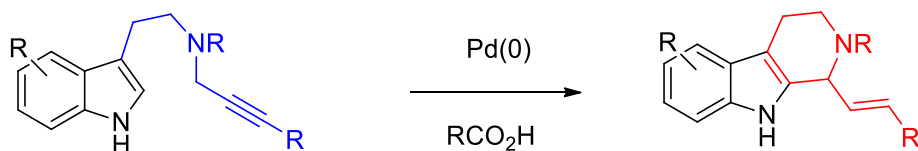


Figure 1. Synthesis of tetrahydrocarbolines from the their corresponding propargylated tryptamines

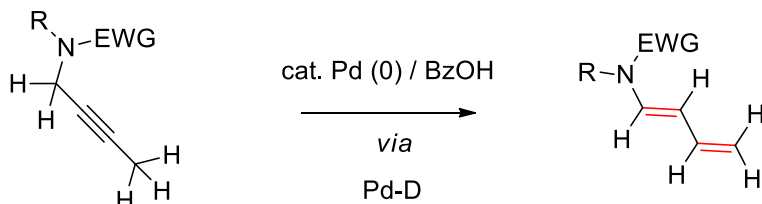


Figure 2. Conversion of internal alkynes into 1,3 dienes

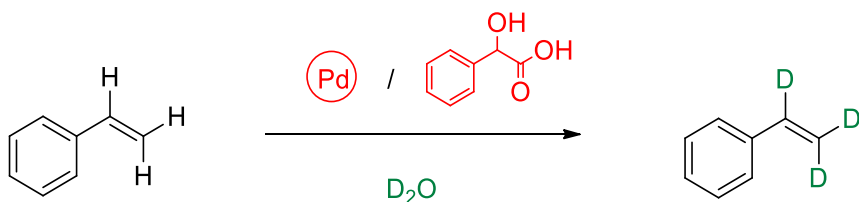
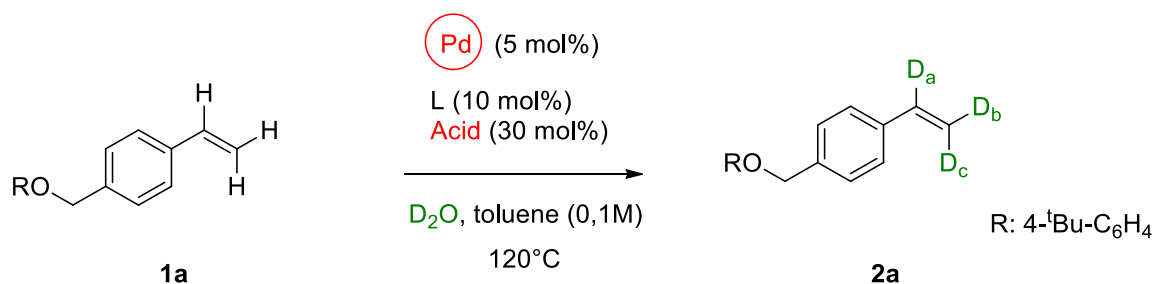


Figure 3. This work

⁴⁰(a) Sattler, A. *ACS Catal.* **2018**, 8, 2296. (b) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. *Angew. Chem. Int. Ed.* **2018**, 57, 3022. (c) Navratil, A. R.; Shchepinov, M. S.; Dennis, E. A. *J. Am. Chem. Soc.* **2018**, 140, 235. (d) Gant, T. G. *J. Med. Chem.* **2014**, 57, 3595. (e) Katsnelson, A. *Nat. Med.* **2013**, 19, 656. (f) Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, 51, 3066. (g) Isin, E. M.; Elmore, C. S.; Nilsson, G. N.; Thompson, R. A.; Weidolf, L. *Chem. Res. Toxicol.* **2012**, 25, 532. (h) Elmore, C. S. *Annu. Rep. Med. Chem.* **2009**, 44, 515. ⁴¹(a) Zarate, C.; Yang, H.; Bezdek, M. J.; Hesk, D.; Chirik, P. J. *J. Am. Chem. Soc.* **2019**, 141, 5034. (b) Kerr, W. J.; Lindsay, D. M.; Owens, P. K.; Reid, M.; Tuttle, T.; Campos, S. *ACS Catal.* **2017**, 7, 7182. (c) Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2014**, 53, 734. (d) Emmert, M. H.; Gary, B. J.; Villalobos, J. M.; Sanford, M. *Angew. Chem. Int. Ed.* **2010**, 49, 5884. (e) Martins, A.; Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, 12, 5186. (f) Pechtl, M. H. G.; Holscher, M.; Ben-David, Y.; Theysen, N.; Loschen, R.; Milstein, D.; Leitner, W. *Angew. Chem. Int. Ed.* **2007**, 46, 2269. ⁴²(a) Muller, V.; Weck, R.; Derdau, V.; Ackermann, L. *Chem. CatChem* **2020**, 12, 100. (b) Valero, M.; Becker, D.; Jess, K.; Weck, R.; Atzrodt, J.; Bannenberg, T.; Derdau, V.; Tamm, M. *Chem. Eur. J.* **2019**, 25, 6517. (c) Valero, M.; Weck, R.; Gussregen, S.; Atzrodt, J.; Derdau, V. *Angew. Chem. Int. Ed.* **2018**, 57, 8159. (d) Kaphan, D. M.; Klet, R. C.; Perras, F. A.; Pruski, M.; Yang, C.; Kropf, J.; Delferro, M. *ACS Catal.* **2018**, 8, 5363. (e) Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; MacMillan, D. W. C. *Science* **2017**, 358, 1182. (f) Pony, Yu. R.; Hesk, D.; Rivera, N.; Pelczar, I.; Chirik, P. J. *Nature* **2016**, 529, 195. ⁴³(a) Trost, B. M.; Tracy, J. S. *ACS Catal.* **2019**, 9, 1584. (b) Wang, J.; Dong, Z.; Yang, C.; Dong, G. *Nat. Chem.* **2019**, 11, 1106. (c) Maestri, G.; Derat, E. *Nat. Chem.* **2019**, 11, 1082. ⁴⁴(a) Puleo, T. R.; Strong, A. J.; Bandar, J. S. *J. Am. Chem. Soc.* **2019**, 141, 1467. (b) Di Giuseppe, A.; Castarlenas, R.; Pérez-Torrente, J. J.; Lahoz, F. J.; Oro, L. A. *Chem. Eur. J.* **2014**, 20, 8391. (c) Hatano, M.; Nishimura, T.; Yorimitsu, H. *Org. Lett.* **2016**, 18, 3674. ⁴⁵(a) Cera, G.; Della Ca', N.; Maestri, G. *Chem. Sci.* **2019**, 10, 10297. (b) Cecchini, C.; Lanzi, M.; Cera, G.; Malacria, M.; Maestri, G. *Synthesis* **2019**, 51, 1216. (c) Lanzi, M.; Cañeque, T.; Marchio, L.; Maggi, R.; Bigi, F.; Malacria, M.; Maestri, G. *ACS Catal.* **2018**, 8, 144. (d) Cera, G.; Lanzi, M.; Balestri, D.; Della Ca', N.; Maggi, R.; Bigi, F.; Malacria, M.; Maestri, G. *Org. Lett.* **2018**, 20, 3220. (e) Cera, G.; Lanzi, M.; Bigi, F.; Maggi, R.; Malacria, M.; Maestri, G. *Chem. Commun.* **2018**, 54, 14021. (f) Monfredini, A.; Santacroce, V.; Marchio, L.; Maggi, R.; Bigi, F.; Maestri, G.; Malacria, M. *ACS Sustainable Chem. Eng.* **2017**, 5, 8205

Results and discussion

We performed a preliminary experiment in which the styrene **1a** was treated with 5 mol% of Pd(PPh₃)₄, 10 mol% of PCy₃, 10 mmol of D₂O and 30 mol% of benzoic acid. The reaction allowed the conversion of **1a** to the corresponding labelled **2a** in 93% displaying good deuteration at β position (63 and 67%, Table 1, entry 1) and minimal incorporation of deuterium at α position (5%). H/D ratio was determined by ¹H NMR by measuring the peaks integrals of starting materials and those of the corresponding deuterated one. The use of a hindered acid gave a similar result (94% of yield, entry 2) but deuterium incorporation was lower (41%, 43% in β position). A fluorine group into the acid decreased slightly the yield (75%, entry 3) but deuterium content rose up to 95% in β position and 10% in α position. 3-chlorobenzoic acid enabled a slightly improvement into the yield and deuterium incorporation (entry 4). 3-iodo benzoic acid proved detrimental (entry 5). Further improvement of the labelling occurred using 3,5 dimethyl benzoic acid (92 % of yield and labelling at α and β positions up to 95%, entry 6). Cinnamic acid was less reactive in terms of yield but enabled excellent deuterium labelling at β position (83 % yield, 92 and 91% of labelling, entry 7). Gratifyingly, mandelic acid allowed both excellent conversion (92% of **2a**) and labelling at α and β positions (entry 8). The absence of PCy₃ decreased the deuterium incorporation at α position to 48% (entry 9). PPh₃ and dppe as ligands proved detrimental in deuterium incorporation (entry 10, 11). Then we tested other palladium catalysts. Whereas Pd(dba)₂ delivered **2a** in excellent yield and good labelling, Pd(OAc)₂ demonstrated to be not tolerant for this reaction (entry 12 and 13, respectively). Mandelic acid seemed to be important for ensuring an excellent conversion and deuterium incorporation into the each -C(sp²)-H of the alkene. Its absence made the reaction inefficient (entry 14).

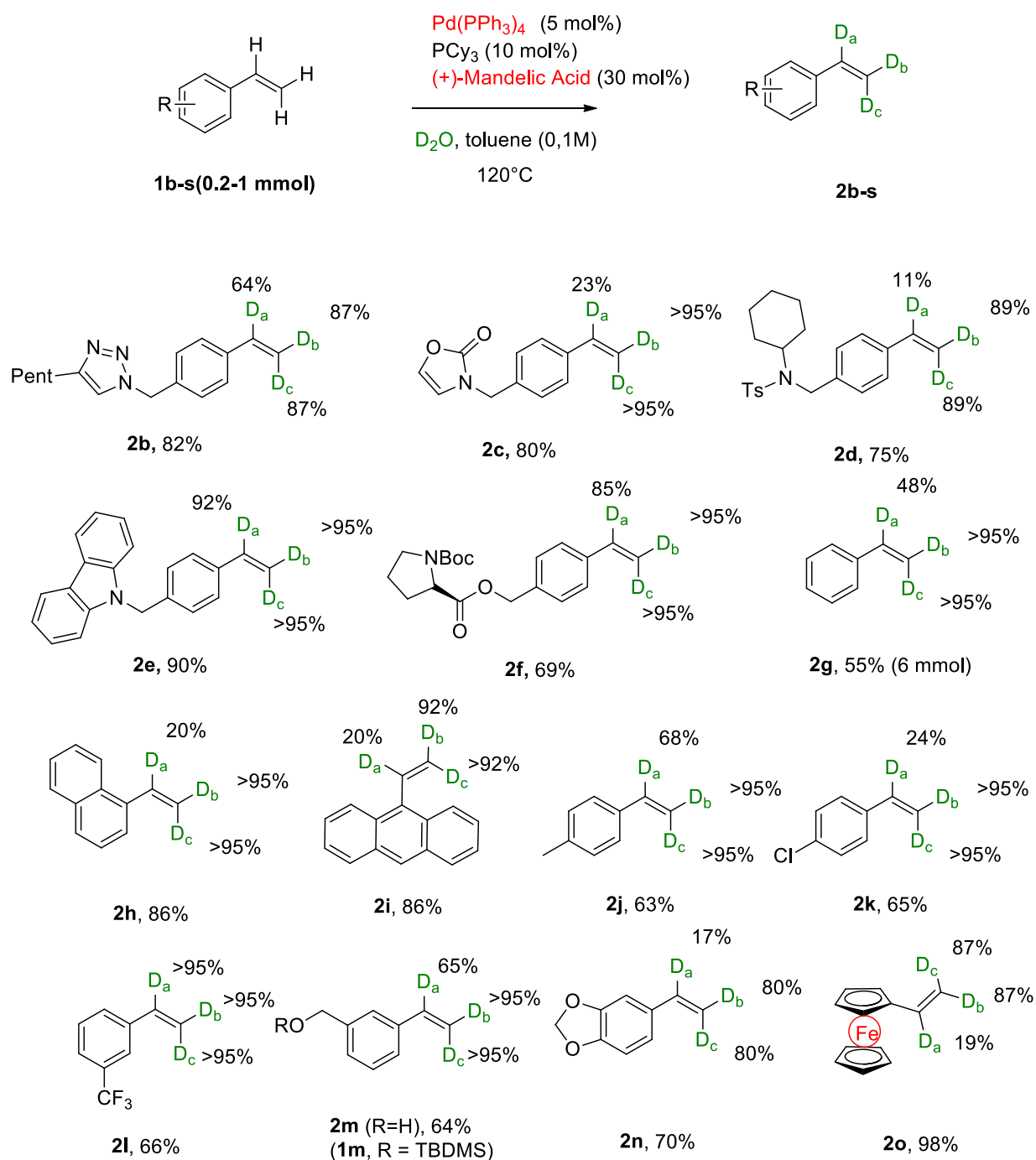


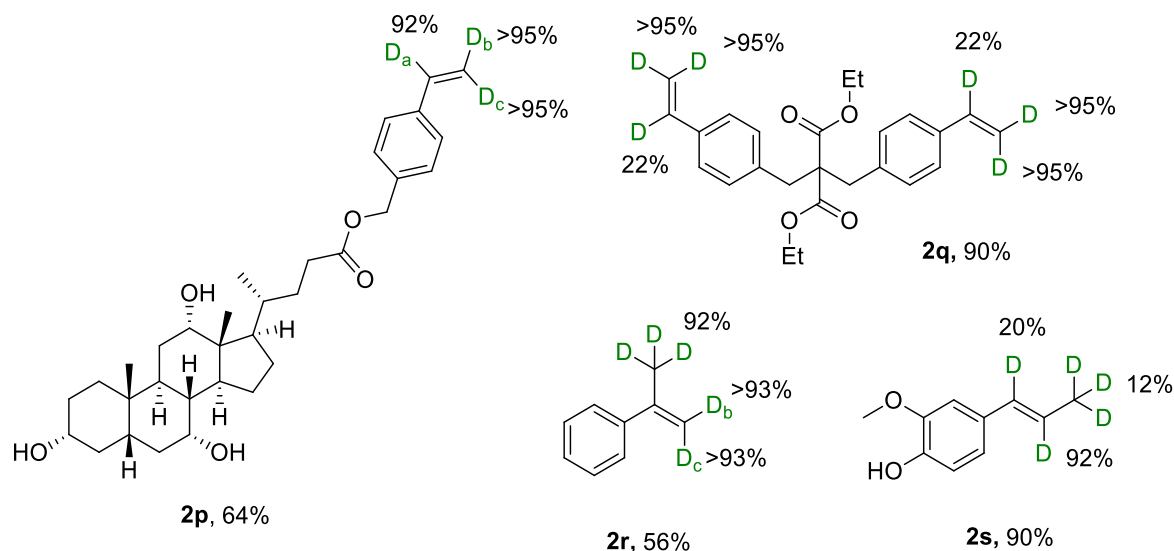
Entry	Pd	L	Acid	Yield %	D _a , D _b , D _c
1	Pd (PPh ₃) ₄	PCy ₃	C ₆ H ₅ CO ₂ H	93	<5, 63, 67
2	Pd (PPh ₃) ₄	PCy ₃	2,4,6-Me ₃ C ₆ H ₂ CO ₂ H	94 ^b	<5, 41, 43
3	Pd (PPh ₃) ₄	PCy ₃	4-FC ₆ H ₄ CO ₂ H	75 ^b	<10, >95, >95
4	Pd (PPh ₃) ₄	PCy ₃	3-ClC ₆ H ₄ CO ₂ H	96	42, >95, >95
5	Pd (PPh ₃) ₄	PCy ₃	3-IC ₆ H ₄ CO ₂ H	78 ^b	<5, <5, <5
6	Pd (PPh ₃) ₄	PCy ₃	3,5-Me ₂ C ₆ H ₃ CO ₂ H	92	80, >95, >95
7	Pd (PPh ₃) ₄	PCy ₃	cinnamic acid	83 ^b	10, 92, 91
8	Pd (PPh ₃) ₄	PCy ₃	(+)-mandelic acid	92	91, >95, >95
9	Pd (PPh ₃) ₄	-	(+)-mandelic acid	90	48, >95, >95
10	Pd (PPh ₃) ₄	PPh ₃	(+)-mandelic acid	77 ^b	41, <10, <10
11	Pd (PPh ₃) ₄	dppe	(+)-mandelic acid	82 ^b	<10, <10, <10
12 ^c	Pd (dba) ₂	PCy ₃	(+)-mandelic acid	93	23, >95, >95
13 ^d	Pd (OAc) ₂	PCy ₃	(+)-mandelic acid	94 ^b	<10, <10, <10
14	Pd (PPh ₃) ₄	PCy ₃	-	73 ^b	<5, 29, 34

Table 1. Optimization of the catalytic method : **a** Reaction conditions: **1a** (0.2 mmol), [Pd] (0.01 mmol), ligand (L) (0.02 mmol), acid (0.06 mmol), D₂O (10 mmol), toluene (2 mL, 0.1 M), 120 °C, 16 h; yields are those of isolated products. **b** NMR yields using 1,3,5-trimethoxybenzene as the internal standard. **c** PCy₃ (0.08 mmol). **d** PCy₃ (0.03 mmol).

With the conditions in our hands we explored a variety of a styrenes in order to deliver their corresponding deuterated species. Triazole in styrene **1b** enabled a good conversion (82%) and excellent deuterium content particularly in β position (87%). Similar results we noticed in **2c** and **2d**, albeit the labelling was much lower in α position (23% and 11%, respectively). Styrenes bearing carbazole (**2e**) and a proline units (**2f**) showed excellent deuterium incorporation in each C(sp²)-H of the alkene. **2g** displayed excellent deuteration at its methylene unit (> 95%, scale-up to 6 mmol) and lower deuterium content at the α position (48%). Extended aromatic rings such as naphthalene (**2h**) and anthracene (**2i**) were isolated in excellent yield (86% and 90%, respectively) and with remarkable deuterium labelling at their methylene units (92%). Electron rich (**2m**) and electron withdrawing groups (**2l**) into the

aromatic ring did not influence the yield (64% and 66% respectively). However labelling at α position in **2l** was higher than in **2m** ($>95\%$). **2n** and **2o** displayed negligible deuterium labelling at α position (17% and 19% respectively). The yield of deuterated colic acid derivative was not so excellent (**2p**, 64%) but the deuteration content at α and β positions was remarkable (92% and $>95\%$ respectively). Styrene dimer such as **1q** displayed superb deuterium content at their methylene units ($>95\%$) but low labelling at the α position (22%). Finally we employed α -methyl styrene (**1r**) and isoeugenol (**1s**). Gratifyingly, α -methyl styrene showed remarkable deuterium content at both methylene group (93%) and methyl one (92%). On the contrary **2s** featured good labelling only at the $C(sp^2)$ -H in β position (92%).





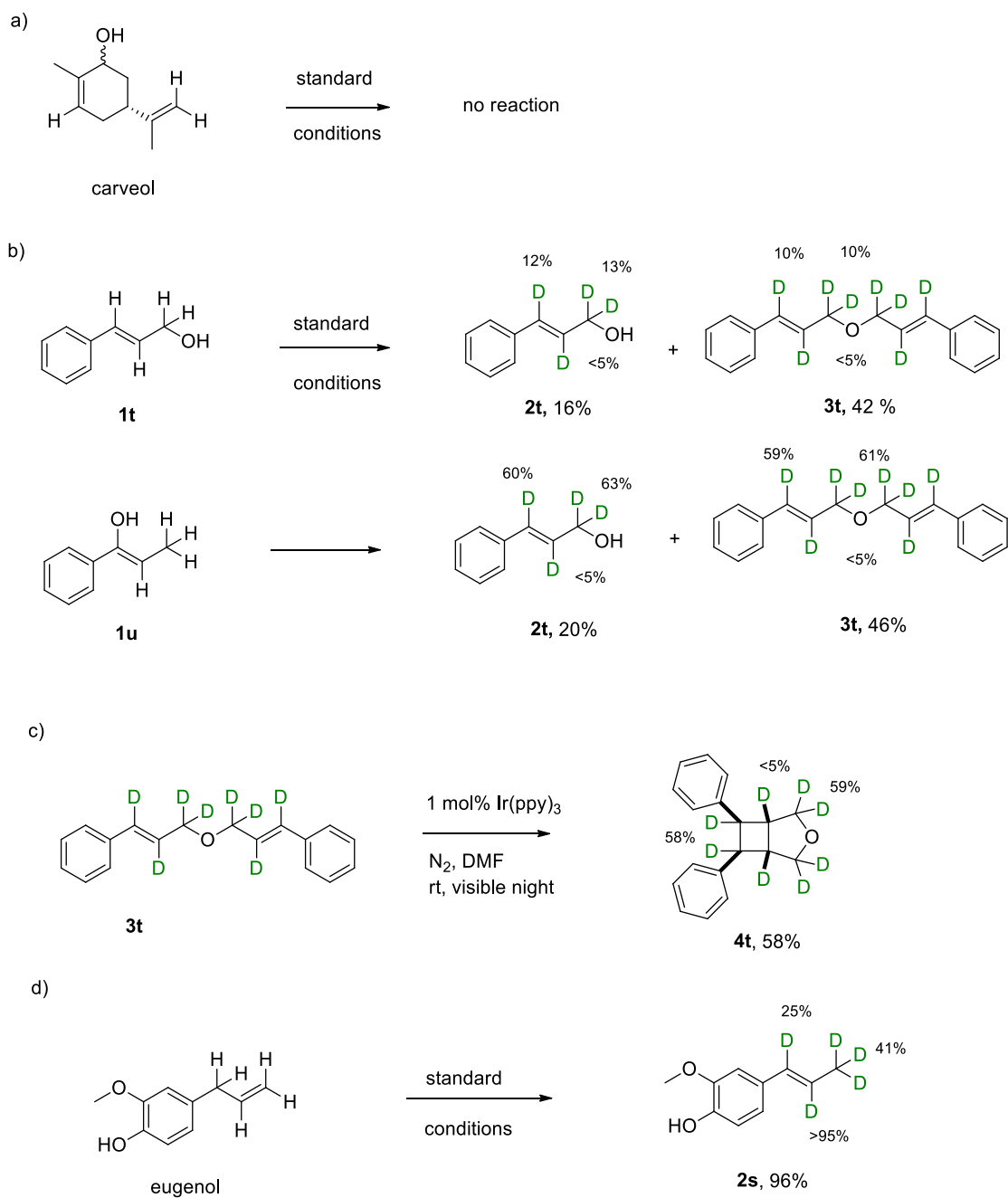
Scheme 2. Scope of the reaction

Afterwards we performed additional experiments. Carveol (Scheme 3, a) did not deliver its corresponding deuterated one.

Cinnamyl alcohol (substrate **1t**, Scheme 3, b) afforded **2t** in 16% and surprisingly the ether **3t** in 42%, displaying minimal labelling in each position. We assumed that **3t** might derived from nucleophilic attack of **1t** on π -allyl palladium (II) species. Generally allylic alcohols are less reactive than their corresponding esters or halides toward formation of sigma-allyl species via oxidative addition on Pd(0).⁷ We assumed that mandelic acid in the crude reacts with the alcohol affording its corresponding ester which in presence of Pd(0) reacts more efficiently.^{7g-k}

We tested this hypothesis using **1u** and the reaction provides **2t** and **3t** in very similar yields (20% and 46%, respectively, Scheme 3, b) but deuterium content proved much higher, particularly at C(sp³)-H (63 and 61% respectively). The resulting **3t** was employed for a [2 + 2] photocycloaddition in the presence of an Iridium catalyst affording product **4t** in 58%.⁴⁷ (Scheme 3, c).

Finally we concluded this studies testing eugenol (Scheme 3, d) Surprisingly the reaction produced **2s** in 96%. We assumed that a double bond isomerization occurred after palladium insertion and β elimination. In this case deuteration labelling was slightly higher than that we noticed employing **2s** (See Scheme 2, **2s**). This result confirms the higher reactivity of terminal olefins compared to that of internal ones.



Scheme 3. Outcomes with substituted allyl fragments enabling access to polydeuterated polycycles

Chem. Eng. **2017**, 5, 8205. ⁴⁶ (a) Zheng, P.; Wang, C.; Chen, Y.-C.; Dong, G. *ACS Catal.* **2019**, 9, 5515. (b) Haydl, A. M.; Breit, B.; Lang, T.; Krische, M. J. *Angew. Chem. Int. Ed.* **2017**, 56, 11312. (c) McCammant, M.; Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, 135, 4167. (d) Lichtenberg, C.; Okuda, J. *Angew. Chem. Int. Ed.* **2013**, 52, 5228. (e) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, 47, 258. (f) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 103, 2921. For selected examples involving allylic alcohols, see: (g) Liu, Q.; Wu, L.; Jiao, H.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* **2013**, 52, 8064. (h) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *Adv. Synth. Catal.* **2006**, 348, 1101. (i) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H.; Yoshifuji, M. *Organometallics* **2004**, 23, 1698. (j) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Mol. Catal. A: Chem.* **1996**, 111, 43. ⁴⁷ (a) Lu, Z.; Yoon, T. P. *Angew. Chem. Int. Ed.* **2012**, 51, 10329. (b) Poplata, S.; Troster, A.; Zou, Y.-Q.; Bach, T. *Chem. Rev.* **2016**, 116, 9748

Conclusion

We reported a method for the preparation of deuterated styrenes starting from their corresponding styrenes in presence of $\text{Pd}(\text{PPh}_3)_4$ and the cheapest and most sustainable source of deuterium D_2O . According to experiments, this method displays ample functional group tolerance. We hope that this method could be regarded as useful synthetic strategy for future investigations.

Experimental section

General Remarks

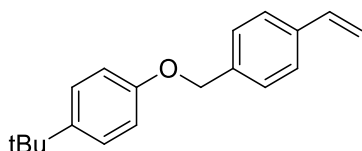
All chemicals those syntheses are not reported hereafter were purchased from commercial sources and used as received. Solvents were dried and stored over molecular sieves previously activated in an oven (450 °C overnight). Chromatographic purifications were performed under gradient using a Combiflash® system and prepacked disposable silica cartridges. ¹H and ¹³C-NMR spectra were recorded at 300 K on a Bruker 400 MHz or Bruker 300 MHz spectrometer using solvent residual signals as internal standards (7.26 ppm for ¹H NMR and 77.00 ppm for ¹³C NMR using CDCl₃). ²H-NMR spectra were recorded at 300 K on a Bruker 400 MHz spectrometer using the corresponding protic solvents. ¹⁹F NMR spectra were recorded in CDCl₃ at 298 K on a JEOL 600 MHz spectrometer fitted with a BBFO probe at 565 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. MS analyses were collected on an Infusion Water Acquity Ultra Performance LC H06UPS823M instrument equipped with SQ detector (ESI source) and on a Thermo GC-MS instrument equipped with SQ detector (EI source). The percentage of deuterium incorporation was determined by integrating a CH₂ [(multiplicity, 2H)*ref*] assumed to have a value of 2.0 or a CH peak [(multiplicity, 1H)*ref*] assumed to have a value of 1.0, with respect to the residual proton signals of the partly deuterated carbons. The reference peak (underline) is given for each spectrum. The percentage of deuterium incorporation was further validated by integrating ²H NMR signals to the calibrated deuterium signals, whose value has been previously determined by ¹H NMR. Values determined by NMR analyses were then compared with MS ones, showing good correlation between the two techniques.

Synthesis of Styrenes

General procedure A

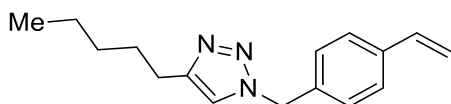
In a 100 mL round-bottom flask equipped with a stir bar, methyltriphenylphosphonium bromide (1.2 equiv.) was dissolved in 50 ml THF under N₂ atmosphere. Then, *n*-BuLi (1.2 equiv) was added dropwise at 0 °C (ice bath) and the mixture was stirred for 15 minutes. The aldehyde was dissolved in 10 ml of THF and the solution was then syringed through a septum. The mixture was stirred for 1 hour and maintained at 0 °C. It was then allowed to warm to room temperature and maintained under stirring for 9 hours. It was then quenched with water and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with H₂O, brine and dried over by Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give the corresponding alkene.

1-(*tert*-Butyl)-4-[(4-vinylbenzyl)oxy]benzene (**1a**)



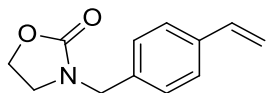
In a Schlenk flask, 1-(chloromethyl)-4-vinylbenzene (670 μ l, 4.8 mmol) was added dropwise to a solution of 4-(*tert*-Butyl)phenol (600 mg, 4.0 mmol) and K₂CO₃ (830 mg, 6.0 mmol) in acetone (10 ml). Subsequently, the mixture was placed in a pre-heated oil bath at 60 °C and stirred overnight. After completion, the reaction mixture was cooled down to room temperature and sat. NH₄Cl (15 ml) was added. The mixture was extracted with EtOAc (3 x 15 ml), the organic layers separated and dried over Na₂SO₄. The combined fractions were concentrated under reduced pressure and the crude purified by chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielding **1a** (841 mg, 79%) as white solid. M. p. = 80.2 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.49 – 7.41 (m, 4H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 6.77 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.80 (d, *J* = 17.6 Hz, 1H), 5.29 (d, *J* = 10.9 Hz, 1H), 5.07 (s, 2H), 1.34 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ = 156.6 (C_q), 143.7 (C_q), 137.3 (C_q), 136.9 (C_q), 136.5 (CH), 127.7 (CH), 126.4 (CH), 126.3 (CH), 114.3 (CH), 114.0 (CH₂), 69.8 (CH₂), 34.1 (C_q), 31.5 (CH₃). (ESI)-MS calcd for C₁₉H₂₃O [M+H]⁺ 267.18 found 267.16.

4-Pentyl-1-(4-vinylbenzyl)-1*H*-1,2,3-triazole (**1b**)



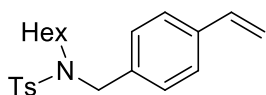
In a round bottomed flask, 1-heptyne (750 μ l, 5.5 mmol) was added to a solution of 1-(azidomethyl)-4-vinylbenzene (795 mg, 5.0 mmol) in *t*-BuOH:H₂O (20:1, 20 ml:1 ml). Subsequently, sodium ascorbate (198 mg, 1.0 mmol) and CuSO₄*5H₂O (124 mg, 0.5 mmol) were added and the mixture stirred overnight. After completion, sat NH₄Cl (30 ml) was added and the mixture was extracted with EtOAc (3 x 20 ml). The combined organic fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (*n*-hexane/EtOAc 95:5→60:40) yielding **1b** (725 mg, 57%) as white solid. M. p. = 75.6 °C. ¹H NMR (300 MHz, CDCl₃) δ = 7.41 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.16 (m, 3H), 6.71 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.77 (d, *J* = 17.4 Hz, 1H), 5.49 (s, 2H), 5.29 (d, *J* = 11.0 Hz, 1H), 2.79 – 2.59 (m, 2H), 1.78 – 1.58 (m, 2H), 1.46 – 1.24 (m, 4H), 1.01 – 0.78 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ = 149.0 (C_q), 138.0 (C_q), 136.0 (CH), 134.4 (C_q), 128.2 (CH), 126.8 (CH), 120.5 (CH), 114.8 (CH₂), 53.7 (CH₂), 31.5 (CH₂), 29.1 (CH₂), 25.7 (CH₂), 22.4 (CH₂), 14.0 (CH₃). (ESI)-MS calcd for C₁₆H₂₂N₃ [M+H]⁺ 256.18 found 256.16.

3-(4-Vinylbenzyl)-oxazolidin-2-one (**1c**)



In a Schlenk flask, under nitrogen atmosphere at 0 °C, NaH (60% in mineral oil) (150 mg, 3.6 mmol) was carefully added to a solution of 5-oxazolidin-2-one (261 mg, 3.0 mmol) in dry DMF (15 ml). After 30 min of stirring, 1-(chloromethyl)-4-vinylbenzene (500 μ l, 3.6 mmol) was added dropwise. The mixture was subsequently placed in a pre-heated oil bath at 60 °C and stirred overnight. After completion, the reaction mixture was cooled down to room temperature and aq. HCl (1.0 M) (20 ml) was added. The mixture was extracted with EtOAc (3 x 20 ml) and the organic layers washed with a sat. LiCl. The combined organic fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (*n*-hexane/EtOAc 80:20→55:45) yielding **1c** (493 mg, 79%) as viscous oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.40 (dd, *J* = 8.1, 2.1 Hz, 2H), 7.25 (dd, *J* = 8.1, 2.1 Hz, 2H), 6.71 (ddd, *J* = 17.7, 11.0, 2.1 Hz, 1H), 5.76 (dd, *J* = 17.6, 2.1 Hz, 1H), 5.27 (dd, *J* = 10.9, 2.1 Hz, 1H), 4.42 (d, *J* = 2.2 Hz, 2H), 4.34 – 4.25 (m, 2H), 3.52 – 3.35 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 158.6 (C_q), 137.4 (CH), 136.2 (C_q), 135.3 (C_q), 128.4 (CH), 126.7 (CH), 114.3 (CH₂), 61.8 (CH₂), 48.1 (CH₂), 43.9 (CH₂). (ESI)-MS calcd for C₁₂H₁₃NNaO₂ [M+Na]⁺ 226.08 found 226.12.

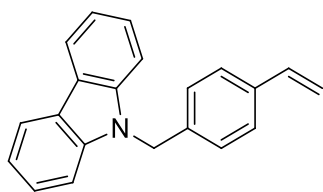
N-Hexyl-4-methyl-*N*-(4-vinylbenzyl)benzenesulfonamide (**1d**)



In a Schlenk flask, 1-(chloromethyl)-4-vinylbenzene (500 μ l, 3.6 mmol) was added dropwise to a solution of *N*-hexyl-4-methylbenzenesulfonamide (611 mg, 2.2 mmol), NaI (500 mg, 3.6 mmol) and K₂CO₃ (540 mg, 3.6 mmol) in acetonitrile (10 ml). Subsequently, the mixture was placed in a pre-heated oil bath at 80 °C and stirred overnight. After completion, the reaction mixture was cooled down to room temperature and sat. NH₄Cl (15 ml) was added. The mixture was extracted with EtOAc (3 x 15 ml), the organic layers separated and dried over Na₂SO₄. The combined fractions were concentrated under reduced pressure and the crude purified by chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielding **1d** (290 mg, 34%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.75 (d, *J* = 7.8 Hz, 2H), 7.35 (dd, *J* = 15.4, 7.8 Hz, 4H), 7.26 (d, *J* = 7.8 Hz, 2H), 6.72 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.76 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 10.9 Hz, 1H), 4.32 (s, 2H), 3.09 (t, *J* = 7.7 Hz, 2H),

2.46 (s, 3H), 1.34 (t, $J = 7.4$ Hz, 2H), 1.23 – 1.04 (m, 6H), 0.82 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.2 (Cq), 137.2 (Cq), 137.1 (Cq), 136.4 (CH), 136.2 (Cq), 129.7 (CH), 128.5 (CH), 127.2 (CH), 126.4 (CH), 114.0 (CH_2), 51.5 (CH_2), 48.1 (CH_2), 31.2 (CH_2), 27.9 (CH_2), 26.3 (CH_2), 22.4 (CH_2), 21.5 (CH_3), 13.9 (CH_3). (ESI)-MS calcd for $\text{C}_{22}\text{H}_{29}\text{NNaO}_2\text{S}$ $[\text{M}+\text{Na}]^+$ 394.18 found 394.14.

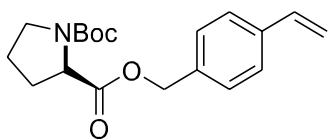
9-(4-Vinylbenzyl)-9H-carbazole (1e)



Analytical data correspond to literature: Polymer, **2014**, 55, 5998-6005.

¹H NMR (400 MHz, CDCl₃) δ = 8.17 (d, J = 7.8 Hz, 2H), 7.50 – 7.43 (m, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.35 – 7.25 (m, 4H), 7.13 (d, J = 7.8 Hz, 2H), 6.69 (dd, J = 17.6, 10.9 Hz, 1H), 5.71 (d, J = 17.6 Hz, 1H), 5.54 (s, 2H), 5.24 (d, J = 10.9 Hz, 1H). **¹³C NMR** (75 MHz, CDCl₃) δ = 140.7 (C_q), 136.9 (C_q), 136.7 (C_q), 136.3 (CH), 126.7 (CH), 126.6 (CH), 125.9 (CH), 123.1 (C_q), 120.4 (CH), 119.3 (CH), 113.9 (CH₂), 108.9 (CH), 46.4 (CH₂). **(ESI)-MS** calcd for C₂₁H₁₇Nna [M+Na]⁺ 306.13 found 306.10.

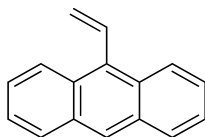
1-(tert-Butyl) 2-(4-vinylbenzyl) (S)-pyrrolidine-1,2-dicarboxylate (1f)



In a oven dried Schlenk flask, 1-(Chloromethyl)-4-vinylbenzene (330 μ l, 2.4 mmol) was added dropwise to a solution of (tert-butoxycarbonyl)-L-proline (430 mg, 2.0 mmol) and Na₂CO₃ (210 mg, 2.0 mmol) in DMF:H₂O (10:1, 15ml:150 μ l). The mixture was subsequently placed in a pre-heated oil bath at 60 °C and stirred overnight. After completion, the reaction mixture was cooled down to room temperature and aq. HCl (1.0 M) (20 ml) was added. The mixture was extracted with EtOAc (3 x 20 ml) and the organic layers washed with a sat. LiCl. The combined organic fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (*n*-hexane/EtOAc 95:5 $\rightarrow$ 60:40) yielding **1f** (563 mg, 85%) as viscous oil. **¹H NMR** (300 MHz, CDCl₃) δ = 7.43– 7.38 (m, 2H), 7.36 – 7.30 (m, 2H), 6.73 (dd, J = 17.6, 10.9 Hz, 1H), 5.77 (d, J = 17.6 Hz, 1H), 5.39 – 4.99 (m, 3H), 4.40 (dd, J = 8.5, 3.5 Hz, RotA), 4.28 (dd, J = 8.5, 3.5 Hz, RotB), 3.72 – 3.29 (m, 1H), 2.22 (q, J = 7.1, 5.9 Hz, 1H), 2.02 – 1.83 (m, 3H), 1.48 (s, 3H), 1.36 (s, 6H). **¹³C NMR**

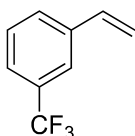
NMR (75 MHz, CDCl₃) δ = 173.1 (rotA, C_q), 172.8 (rotB, C_q), 154.5 (rotB, C_q), 153.8 (rotA, C_q), 137.7 (rotA, C_q), 137.5 (rotB, C_q), 136.4 (rotB, CH), 136.3 (rotA, CH), 135.4 (rotB, C_q), 135.1 (rotA, C_q), 128.6 (rotA, CH), 128.3 (rotB, CH), 126.4 (rotA, CH), 126.3 (rotB, CH), 114.4 (rotA, CH₂), 114.2 (rotB, CH₂), 79.9 (rotA, C_q), 79.8 (rotB, C_q), 66.4 (rotA+B, CH), 59.2 (rotA, CH₂), 58.9 (rotB, CH₂), 46.6 (rotB, CH₂), 46.3 (rotA, CH₂), 30.9 (rotA, CH₂), 29.9 (rotB, CH₂), 28.4 (CH₃), 28.2 (2xCH₃), 24.3 (rotB, CH₂), 23.6 (rotA, CH₂). **(ESI)-MS** calcd for C₁₉H₂₆NO₄ [M+H]⁺ 332.19 found 332.15.

9-vinylanthracene (1i)



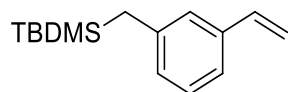
Representative procedure A was followed using anthracene-9-carbaldehyde (200 mg, 0.97mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 8:2) yielded the corresponding alkene (88.5 mg, 44%) as pale yellow oil. **¹H NMR** (400 MHz, CDCl₃) δ = 8.40 (s, 1H), 8.33 (m, 2H), 8.00 (dd, *J* = 3.55, 6.24 Hz, 2H), 7.47 (dd, *J* = 3.23, 6.71 Hz, 5H), 6.02 (dd, *J* = 2.09, 11.46 Hz, 1H), 5.64 (dd, *J* = 2.09, 17.88 Hz, 1H) **¹³C NMR** (101 MHz, CDCl₃) δ = 133.8 (C_q), 133.7 (CH), 131.5 (2C_q), 129.3 (2C_q), 128.7 (2CH), 126.5 (CH), 126.1 (2CH), 125.5 (2CH), 125.2 (2CH), 123.1 (CH₂).

1-(trifluoromethyl)-3-vinylbenzene (1l)



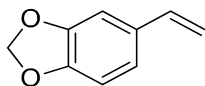
Representative procedure A was followed using 3-(trifluoromethyl)benzaldehyde (1g, 5.74 mmol). Purification by column chromatography on silica gel (*n*-pentane) yielded the corresponding alkene (361.7 mg, 37%) as colorless liquid. **¹H NMR** (400MHz, CDCl₃) δ = 7.64 (s, 1H), 7.58 (d, *J* = 7.60 Hz, 1H), 7.51 (d, *J* = 7.71 Hz, 1H), 7.44 (t, *J* = 7.69 Hz, 1H), 6.75 (dd, *J* = 10.90, 17.59 Hz, 1H), 5.83 (d, *J* = 17.58 Hz, 1H), 5.36 (d, *J* = 10.91 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 138.4 (C_q), 135.7 (CH), 131.1 (q, *J* = 32.25Hz, C_q), 129.5 (d, *J* = 1.24 Hz, CH), 129.1 (CH), 124.4 (q, *J* = 3.64, CH), 124.3 (q, *J* = 273.71 Hz, C_q), 123.1 (q, *J* = 3.96 Hz, CH), 115.9 (CH₂). **¹⁹F NMR** (565 MHz, CDCl₃) δ = -62.7 (s).

tert-butyltrimethylsilyl((3-vinylbenzyl)oxy)silane (**1m**)



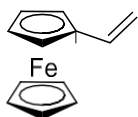
In a oven dried Schlenk flask, tert-butylchlorodimethylsilane (550 mg, 3.3 mmol) was added to a solution of (3-vinylphenyl)methanol (400 mg, 3.0 mmol) and imidazole (224 mg, 3.3 mmol) in DMF (10 ml). The mixture was stirred for 1 h. After completion, H₂O (20 ml) was added. The mixture was extracted with EtOAc (3 x 20 ml) and the organic layers washed with a sat. LiCl solution. The combined organic fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (*n*-hexane/EtOAc 95:5→80:20) yielding **1m** (455 mg, 61%) as viscous oil. ¹H NMR (300 MHz, CDCl₃) δ 7.42 (s, 1H), 7.36 – 7.30 (m, 2H), 7.29 – 7.23 (m, 1H), 6.76 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.78 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.27 (dd, *J* = 10.9, 1.0 Hz, 1H), 4.78 (s, 2H), 0.99 (s, 9H), 0.15 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ = 141.7 (C_q), 137.5 (C_q), 137.0 (CH), 128.4 (CH), 125.5 (CH), 124.9 (CH), 123.8 (CH), 113.7 (CH₂), 64.9 (CH₂), 26.0 (CH₃), 18.5 (C_q), -5.2 (CH₃). (ESI)-MS calcd for C₁₅H₂₄NaOSi [M+Na]⁺ 271.15 found 271.19.

5-vinylbenzo[d][1,3]dioxole (1n)



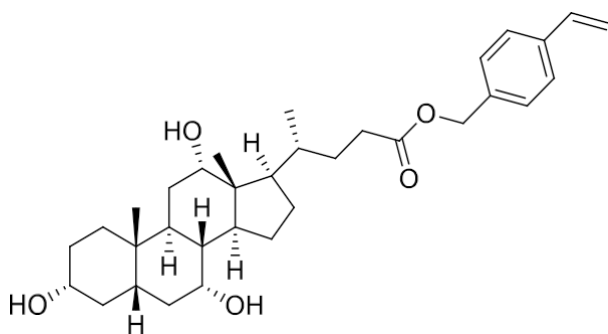
Representative procedure A was followed using benzo[d][1,3]dioxole-5-carbaldehyde (720 mg, 5 mmol). Purification by column chromatography on silica gel (*n*-hexane 9.5/EtOAc 0.5) yielded the corresponding alkene (196.4 mg, 27%) as colorless liquid. **¹H NMR** (400MHz, CDCl₃) δ = 6.96 (d, *J* = 1.65 Hz, 1H), 6.83 (dd, *J* = 1.60, 7.99 Hz, 1H), 6.76 (d, *J* = 7.98Hz, 1H), 6.62 (dd, *J* = 10.84, 17.53 Hz, 1H), 5.96 (s, 2H), 5.58 (dd, *J* = 0.65, 17.52 Hz, 1H), 5.13 (dd, *J* = 0.55, 10.85, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 148.1 (C_q), 147.4 (C_q), 136.4 (CH), 132.2 (C_q), 121.1 (CH), 112.1 (CH₂), 108.3 (CH), 105.5 (CH), 101.2 (CH₂).

Vinylferrocene (1o)



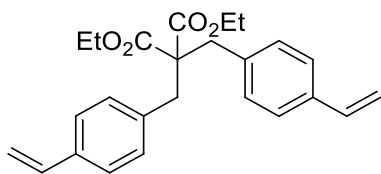
Representative procedure A was followed using ferrocenecarboxaldehyde (624 mg, 3 mmol) in THF (15 ml). Purification by column chromatography on silica gel (*n*-hexane) yielded **1o** (171 mg, 27 %) as red solid. **¹H NMR** (400 MHz, CDCl₃) δ = 6.45 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.34 (d, *J* = 17.6, 1H), 5.02 (d, *J* = 10.7, 1H), 4.36 (s, 2H), 4.21 (s, 2H), 4.10 (s, 5H). **¹³C NMR** (75 MHz, CDCl₃) δ = 134.7 (CH), 111.1 (CH₂), 83.6 (C_q), 69.2 (5CH), 68.7 (2CH), 66.69 (2CH). **(ESI)-MS** calcd for C₁₂H₁₂Fe [M]⁺ 212.03 found 211.95.

(R)-4-vinylbenzyl-4-((3R,5S,7R,8R,9S,10S,12S,13R,14S,17R)-3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (1p)



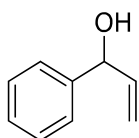
In a Schlenk flask, 1-(chloromethyl)-4-vinylbenzene (200 μ l, 1.3 mmol) was added dropwise to a solution of colic acid (408 mg, 1 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in DMF (2 ml). Subsequently, the mixture was placed in a pre-heated oil bath at 60 $^{\circ}C$ and stirred overnight. After completion, the reaction mixture was cooled down to room temperature and H_2O (10 ml) was added. The mixture was extracted with EtOAc (3 x 10 ml), the organic layers separated and dried over Na_2SO_4 . The combined fractions were concentrated under reduced pressure and the crude purified by chromatography on silica gel (DCM/MeOH 99:1-97:3) yielding **1p** (477 mg, 91%) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.71 (dd, J = 17.6, 10.9 Hz, 1H), 5.75 (d, J = 17.6 Hz, 1H), 5.26 (d, J = 10.9 Hz, 1H), 5.13-5.04 (m, 2H), 3.98-3.93 (m, 1H), 3.84 (q, J = 3.0 Hz, 1H), 3.50-3.40 (m, 1H), 2.47-2.00 (m, 7H), 1.99-1.18 (m, 18H), 1.17- 1.03 (m, 1H), 1.03-0.92 (m, 4H), 0.91-0.84 (m, 3H), 0.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.3 (C_q), 137.5 (C_q), 136.4 (CH), 135.4 (C_q), 128.5 (2CH), 126.4 (2CH), 114.3 (CH_2), 73.1 (CH), 71.9 (CH), 68.4 (CH), 65.8 (CH_2), 46.9 (CH), 41.5 (CH), 41.5 (CH), 39.5 (CH_2), 39.3 (CH), 35.3 (CH, CH_2), 34.8 (CH_2), 34.8 (C_q), 31.4 (CH_2), 30.9 (CH_2), 30.4 (CH_2), 28.2 (CH_2), 27.6 (CH_2), 26.2 (CH), 23.3 (CH_2), 22.5 (CH_3), 17.3 (CH_3), 14.2 (C_q), 12.5 (CH_3). (ESI)-MS calcd for $C_{33}H_{48}NaO_5$ $[M+Na]^+$ 547.34 found 547.37.

Diethyl 2,2-bis(4-vinylbenzyl)malonate (1q)



¹H NMR (300 MHz, CDCl₃) δ = 7.35 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.71 (dd, J = 17.6, 10.9 Hz, 1H), 5.75 (dd, J = 17.6, 1.0 Hz, 1H), 5.25 (dd, J = 10.9, 0.9 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.24 (s, 2H), 1.20 (t, J = 7.2 Hz, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ = 170.9 (C_q), 136.5 (C_q), 136.3 (C_q), 136.0 (CH), 130.3 (CH), 126.1 (CH), 113.6 (CH₂), 61.3 (CH₂), 60.1 (C_q), 38.9 (CH₂), 13.9 (CH₃). **(ESI)-MS** calcd for C₂₅H₂₈NaO₄ [M+Na]⁺ 415.19 found 415.17.

1-phenylprop-2-en-1-ol (1t)

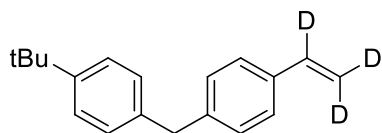


In a Schlenk flask, a vinylmagnesium chloride solution (1.6 M in THF, 7 ml, 11.2 mmol) was added dropwise to a solution of distilled benzaldehyde (1.1 g, 10 mmol) in THF (40 ml) at -10° C. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The mixture was quenched with water (20 ml) and extracted with diethyl ether (3 x 30 ml). The combined organic fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (*n*-hexane/EtOAc 9:1-→8:2) yielding **1t** (1.27 g, 95%) as clear oil. **¹H NMR** (400 MHz, CDCl₃) δ = 7.42-7.27 (m, 5H), 6.12 – 6.00 (m, 1H), 5.36 (d, J = 17.1, 1H), 5.26-5.16 (m, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ = 142.6 (C_q), 140.2 (CH), 128.6(2CH), 127.8 (CH), 126.3 (2CH), 115.2(CH₂), 75.4 (CH). **(ESI)-MS** calcd for C₂₇H₂₇KO₃ [3M+K]⁺ 441.18 found 441.29.

Catalytic Deuteration of Styrenes; General Procedure

In a glass tube, alkene **1** (0.20 mmol), Pd(PPh₃)₄ (0.01 mmol), PCy₃ (0.02 mmol) and (+)-mandelic acid (0.06 mmol) were added sequentially and the tube was then purged with nitrogen three times. Subsequently, toluene (2.0 mL, 0.1 M) and D₂O (10 mmol) were added under a N₂ atmosphere and the tube was placed in a pre-heated oil bath at 120 °C and the contents stirred overnight (16 h). The reaction mixture was then cooled to room temperature and diluted with CH₂Cl₂ (10 mL). The mixture was directly concentrated under reduced pressure and the crude residue was purified by chromatography on silica gel. H/D ratio for each C(sp²) of the alkene was determined by ¹H NMR by comparing the peaks integrals of the starting materials and those of the corresponding deuterated ones.

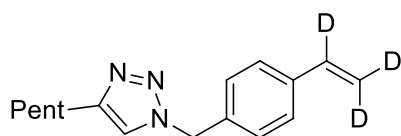
1-(tert-Butyl)-4-{[4-(vinyl-*d*₃)benzyl]oxy}benzene (**2a**)



Da: 91, Db > 95, Dc > 95

Product **2a** was isolated as a white solid (49.5 mg, 92%) using **1a** (53.2 mg, 0.20 mmol) as the reagent. ¹H NMR (400 MHz, CDCl₃): d = 7.49–7.41 (m, 4 H), 7.39–7.31 (m, 2 H), 6.95 (d, *J* = 8.3 Hz, 2 H), 6.75 (s, 0.09 H), 5.78 (s, 0.03 H), 5.26 (s, 0.05 H), 5.07 (s, 2 H, ref), 1.33 (s, 9 H). ¹³C NMR (101 MHz, CDCl₃): d = 156.6 (Cq), 143.7 (Cq), 137.2 (Cq), 136.9 (CD), 136.5 (Cq), 127.7 (CH), 126.4 (CH), 126.3 (CH), 114.3 (CH), 114.0 (CD₂, weak), 69.8 (CH₂), 34.1 (Cq), 31.6 (CH₃). ²H NMR (61 MHz, CHCl₃): d = 6.77 (s, 0.90 D), 5.73 (s, 1 D), 5.24 (s, 1 D). MS (ESI): *m/z* [M + H]⁺ calcd for C₁₉H₂₀D₃O: 270.19; found: 270.11 (100%). MS (ESI): *m/z* [M + H]⁺ calcd for C₁₉H₂₁D₂O: 269.19; found: 269.09 (34%). MS (ESI): *m/z* [M + H]⁺ calcd for C₁₉H₂₂DO: 268.18; found: 268.08 (19%). Average deuterium content for *d*-**2a** calculated from the isotopic abundance of MS analyses: 2.30.

4-Pentyl-1-[4-(vinyl-*d*₃)benzyl]-1H-1,2,3-triazole (**2b**)

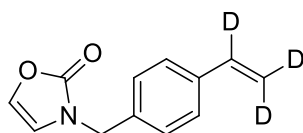


2b, 82%

Da: 64%, Db: 87%, Dc: 87%

Product **2b** was isolated as a white solid (63.9 mg, 82%) using **1b** (76.5 mg, 0.3 mmol) as the reagent. **¹H NMR** (300 MHz, CDCl₃): δ = 7.43–7.38 (m, 2 H), 7.29–7.19 (m, 3 H), 6.71–6.68 (m, 0.36 H), 5.79–5.72 (m, 0.13 H), 5.49–4.45 (m, 2 H, ref), 5.29–5.26 (m, 0.13 H), 2.72–2.66 (m, 2 H), 1.70–1.60 (m, 2 H), 1.38–1.25 (m, 4 H), 0.93–0.84 (m, 3 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 149.0 (Cq), 138.0 (Cq), 135.8 (CD), 134.4 (Cq), 128.2 (CH), 126.8 (CH), 120.5 (CH), 114.3 (CD₂), 53.7 (CH₂), 31.4 (CH₂), 29.1 (CH₂), 25.7 (CH₂), 22.4 (CH₂), 14.0 (CH₃). **²H NMR** (61 MHz, CHCl₃): δ = 6.71 (s, 0.66 D), 5.76 (s, 1 D), 5.30 (s, 1 D). **MS (ESI)**: m/z [M + H]⁺ calcd for C₁₆H₁₉D₃N₃: 259.20; found: 259.28 (100%). **MS (ESI)**: m/z [M + H]⁺ calcd for C₁₆H₂₀D₂N₃: 258.20; found: 258.29 (69%). **MS (ESI)**: m/z [M + H]⁺ calcd for C₁₆H₂₁DN₃: 257.19; found: 257.28 (13%). Average deuterium content for *d*-**2b** calculated from the isotopic abundance of MS analyses: 2.56

3-[4-(Vinyl-*d*₃)benzyl]oxazolidin-2-one (**2c**)

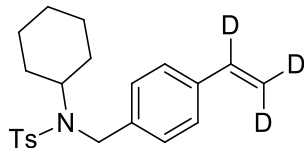


Da: 23%. Db >95%, Dc: >95%

Product **2c** was isolated as a viscous oil (66.9 mg, 80%) using **1c** (83.2 mg, 0.40 mmol) as the reagent. **¹H NMR** (400 MHz, CDCl₃): δ = 7.41 (dd, J = 8.0, 2.1 Hz, 2 H), 7.26 (d, J = 7.8 Hz, 2 H), 6.73–6.67 (m, 0.77 H), 5.79–5.71 (m, 0.03 H), 5.36–5.23 (m, 0.04 H), 4.43 (d, J = 2.0 Hz, 2 H, ref), 4.35–4.28 (m, 2 H), 3.54–3.32 (m, 2 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 158.6 (Cq), 137.4 (CD), 136.1 (Cq), 135.3 (Cq), 128.5 (CH), 126.7 (CH), 114.2 (CD₂), 61.8 (CH₂), 48.2 (CH₂), 43.9 (CH₂). **²H NMR** (61 MHz, CHCl₃): δ = 6.73 (0.23 D), 5.75 (1 D), 5.26 (1 D). **MS (ESI)**: m/z [M + Na]⁺ calcd for C₁₂H₁₁D₂NNaO₂: 228.10; found: 228.18 (100%). **MS (ESI)**: m/z [M + Na]⁺ calcd for C₁₂H₁₀D₃NNaO₂: 229.10; found: 229.02 (35%). **MS (ESI)**: m/z [M + Na]⁺ calcd for C₁₂H₁₂DNNaO₂:

227.09; found: 227.00 (27%). Average deuterium content for *d*-**2c** calculated from the isotopic abundance of MS analyses: 2.00.

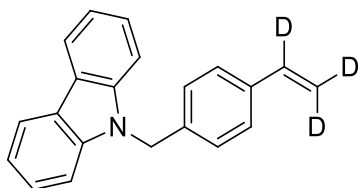
N-Hexyl-4-methyl-N-[4-(vinyl-*d*₃)benzyl]benzenesulfonamide (2d)



Da: 11%, Db: 89%, Dc: 89%

Product **2d** was isolated as a yellow oil (58.4 mg, 75%) using **1d** (77.0 mg, 0.2 mmol) as the reagent. **¹H NMR** (400 MHz, CDCl₃): δ = 7.75 (d, *J* = 7.9 Hz, 2 H), 7.40–7.30 (m, 4 H), 7.29–7.23 (m, 2 H), 6.71 (s, 0.89 H), 5.74 (d, *J* = 17.6 Hz, 0.11 H), 5.25 (d, *J* = 10.9 Hz, 0.11 H), 4.32 (s, 2 H, ref), 3.12–3.05 (m, 2 H), 2.46 (s, 3 H), 1.36–1.28 (m, 2 H), 1.20–1.07 (m, 6 H), 0.82 (t, *J* = 7.0 Hz, 3 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 143.1 (Cq), 137.2 (Cq), 137.1 (Cq), 136.2 (CH), 136.18 (Cq), 129.7 (CH), 128.5 (CH), 127.19 (CH), 126.3 (CH), 114.0 (CD₂), 51.5 (CH₂), 48.0 (CH₂), 31.2 (CH₂), 27.8 (CH₂), 26.3 (CH₂), 22.4 (CH₃), 21.5 (CH₃). **²H NMR** (61 MHz, CHCl₃): δ = 6.76 (s, 0.03 D), 5.74 (s, 1 D), 5.26 (s, 1 D). **MS (ESI)**: *m/z* [M + H]⁺ calcd for C₂₂H₂₈D₂NO₂S: 374.21; found: 374.19 (100%). **MS (ESI)**: *m/z* [M + H]⁺ calcd for C₂₂H₂₇D₃NO₂S: 375.21; found: 375.18 (29%). **MS (ESI)**: *m/z* [M + H]⁺ calcd for C₂₂H₂₉DNO₂S: 373.20; found: 373.20 (20%). Average deuterium content for *d*-**2d** calculated from the isotopic abundance of MS analyses: 2.06.

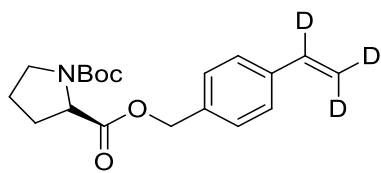
9-[4-(Vinyl-*d*₃)benzyl]-9H-carbazole (**2e**)



Da: 92%, Db>95%, Dc>95

Product **2e** was isolated as a white solid (51.2 mg, 90%) using **1e** (56.6 mg, 0.2 mmol) as the reagent. **¹H NMR** (300 MHz, CDCl₃): δ = 8.18 (d, J = 7.7 Hz, 2 H), 7.51–7.25 (m, 8 H), 7.13 (d, J = 8.0 Hz, 2 H), 6.68 (s, 0.08 H), 5.75–5.70 (m, 0.04 H), 5.53 (s, 2 H, ref), 5.29–5.23 (m, 0.04 H). **¹³C NMR** (75 MHz, CDCl₃): δ = 140.7 (Cq), 136.9 (Cq), 136.7 (Cq), 136.3 (CD), 126.7 (CH), 126.6 (CH), 125.9 (CH), 123.1 (Cq), 120.4 (CH), 119.3 (CH), 113.9 (CD₂), 108.9 (CH), 46.4 (CH₂). **²H NMR** (61 MHz, CHCl₃): δ = 6.65 (s, 0.87 D), 5.60 (s, 1 D), 5.16 (s, 1 D). **MS (ESI)**: m/z [M + Na]⁺ calcd for C₂₁H₁₄D₃NNa: 309.14; found: 309.06 (100%). **MS (ESI)**: m/z [M + Na]⁺ calcd for C₂₁H₁₅D₂NNa: 308.14; found: 308.10 (36%). **MS (ESI)**: m/z [M + Na]⁺ calcd for C₂₁H₁₆DNNa: 307.13; found: 307.19 (15%). Average deuterium content for *d*-**2e** calculated from the isotopic abundance of MS analyses: 2.56.

1-(tert-Butyl) 2-[4-(Vinyl-*d*₃)benzyl] (S)-Pyrrolidine-1,2-dicarboxylate (2f)

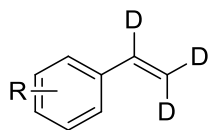


Da: 85%, Db > 95%, Dc > 95%

Product **2f** was isolated as a viscous oil (46.4 mg, 69%) using **1e** (66.2 mg, 0.2 mmol) as the reagent.

¹H NMR (300 MHz, CDCl₃): δ = 7.44–7.33 (m, 2 H, ref), 7.32–7.28 (m, 2 H), 6.70 (s, 0.15 H), 5.74 (s, 0.03 H), 5.32–5.05 (m, 2 H), 4.40 (dd, *J* = 8.6, 3.6 Hz, 1 H, rot A), 4.28 (dd, *J* = 8.6, 3.6 Hz, 1 H, rot B), 3.62–3.40 (m, 2 H), 2.30–2.15 (m, 1 H), 2.05–1.80 (m, 3 H), 1.48 (s, 3 H), 1.36 (s, 6 H). **¹³C NMR** (75 MHz, CDCl₃): δ = 173.1 (Cq, rot A), 172.8 (Cq, rot B), 154.4 (Cq, rot B), 153.8 (Cq, rot A), 137.7 (Cq, rot A), 137.4 (Cq, rot B), 136.4 (CH, rot B), 136.3 (CH, rot A), 135.4 (Cq, rot B), 135.1 (Cq, rot A), 128.6 (CH, rot A), 128.3 (CH, rot B), 126.4 (CH, rot A), 126.3 (CH, rot B), 114.5 (CH₂, rot A), 114.1 (CH₂, rot B), 79.9 (Cq, rot A), 79.8 (Cq, rot B), 66.4 (CH, rot A + B), 59.2 (CH₂, rot A), 58.9 (CH₂, rot B), 46.6 (CH₂, rot B), 46.3 (CH₂, rot A), 30.9 (CH₂, rot A), 29.9 (CH₂, rot B), 28.4 (CH₃), 28.2 (2 CH₃), 24.3 (CH₂, rot B), 23.6 (CH₂, rot A). **²H NMR** (61 MHz, CHCl₃): δ = 6.73 (0.88 D), 5.75 (1 D), 5.26 (1 D). **MS (ESI)**: *m/z* [M + H]⁺ calcd for C₁₉H₂₃D₃NO₄: 335.21; found: 335.29 (100%). **MS (ESI)**: *m/z* [M + H]⁺ calcd for C₁₉H₂₄D₂NO₄: 334.20; found: 334.12 (58%). **MS (ESI)**: *m/z* [M + H]⁺ calcd for C₁₉H₂₅DNO₄: 333.19; found: 333.23 (19%). Average deuterium content for *d*-**2f** calculated from the isotopic abundance of MS analyses: 2.45.

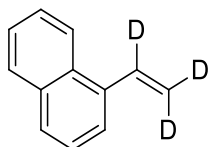
*d*₃-Styrene (**2g**)



Da: 48%, Db > 95%, Db > 95%

Product **2g** was isolated in a 1.1:1 mixture with toluene as a colorless oil (346 mg, 55%) using styrene (624 mg, 6 mmol) as the reagent. **¹H NMR** (400 MHz, CDCl₃): δ = 7.43 (d, *J* = 7.2 Hz, 2 H, ref), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.23–7.14 (m, 1 H), 6.78–6.67 (m, 0.52 H), 5.80–5.72 (m, 0.03 H), 5.27–5.23 (m, 0.03 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 137.9 (CH), 137.5 (CD), 136.7 (Cq), 128.5 (CH), 127.8 (CH), 126.2 (CH), 113.3 (CD₂). **MS (EI)**: *m/z* [M]⁺• calcd for C₈H₅D₃: 107.08; found: 107.16 (67%). **MS (EI)**: *m/z* [M]⁺• calcd for C₈H₆D₂: 106.08; found: 106.16 (100%). **MS (EI)**: *m/z* [M]⁺• calcd for C₈H₇D: 105.08; found: 105.16 (49%). Average deuterium content for *d*-**2g** calculated from the isotopic abundance of MS analyses: 2.08.

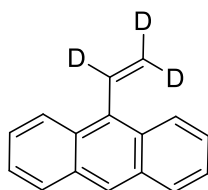
1-(Vinyl-*d*₃)naphthalene (**2h**)



Da: 20%, Db > 95%, Dc > 95%

Product **2h** was isolated as a pale yellow oil (46.6 mg, 88%) using **1e** (50.9 mg, 0.33 mmol) as the reagent. **¹H NMR** (400 MHz, CDCl₃): δ = 8.14 (d, *J* = 8.2, 1.3 Hz, 1 H, ref), 7.89–7.86 (m, 1 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 7.65 (dd, *J* = 7.2, 1.3 Hz, 1 H), 7.56–7.46 (m, 3.27 H), 5.80 (m, 0.03 H), 5.49 (0.03 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 135.5 (Cq), 134.2, 134.1 (CH, CD), 133.6 (Cq), 131.1 (Cq), 128.5 (CH), 128.1 (CH), 126.1 (CH), 125.7 (CH), 123.8 (CH), 123.6 (CH), 123.6 (CH), 116.4 (CD₂). **²H NMR** (61 MHz, CHCl₃): δ = 7.56 (s, 1 D), 5.83 (s, 1 D), 5.49 (s, 1 D). **MS (EI)**: *m/z* [M]⁺• calcd for C₁₂H₇D₃: 157.10; found: 157.20 (82%). **MS (EI)**: *m/z* [M]⁺• calcd for C₁₂H₈D₂: 156.22; found: 156.20 (100%). **MS (EI)**: *m/z* [M]⁺• calcd for C₁₂H₉D: 155.21; found: 155.19 (72%). Average deuterium content for *d*-**2h** calculated from the isotopic abundance of MS analyses: 2.03

9-(Vinyl-d3)-anthracene (2i)

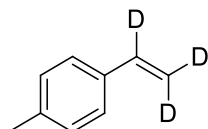


Da: 20%, Db: 92%, Dc > 92%

Product **2i** was isolated as a pale yellow oil (80.6 mg, 90%) using **1i** (88.5 mg, 0.43 mmol) as reagent.

¹H NMR (400 MHz, CDCl₃): δ = 8.39 (s, 1 H, ref), 8.37–8.27 (m, 2 H), 8.06–7.95 (m, 2 H), 7.59–7.36 (m, 4 Ar-H + 0.8 Alk-H), 6.05–5.94 (m, 0.08 H), 5.62 (d, J = 17.9 Hz, 0.08 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 133.4, 134.3 (Cq, CD), 131.5 (2 Cq), 129.4 (2 Cq), 128.7 (2 CH), 126.4 (CH), 126.1 (2 CH), 125.5 (2 CH), 125.2 (2 CH), 116.2 (CD₂). **²H NMR** (61 MHz, CHCl₃): δ = 6.03 (s, 0.89 D), 5.67 (s, 0.92 D). **MS (EI)**: m/z [M]⁺• calcd for C₁₆H₉D₃: 207.11; found: 207.23 (30%). **MS (EI)**: m/z [M]⁺• calcd for C₁₆H₁₀D₂: 206.11; found: 206.24 (91%). **MS (EI)**: m/z [M]⁺• calcd for C₁₆H₁₁D: 205.10; found: 205.24 (100%). Average deuterium content for *d*-**2i** calculated from the isotopic abundance of MS analyses: 1.68.

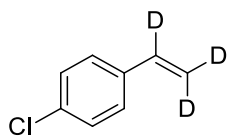
1-Methyl-4-(vinyl-d3)benzene (2j)



Da: 68%, Db > 95%, Dc > 95%

Product **2j** was isolated as a colorless oil (76.6 mg, 63%) using 1-methyl-4-vinylbenzene (118 mg, 1.0 mmol) as the reagent. **¹H NMR** (300 MHz, CDCl₃): δ = 7.35 (d, J = 8.2 Hz, 2 H, ref), 7.17 (d, J = 7.9 Hz, 2 H), 6.78–6.67 (m, 0.32 H), 5.71–5.68 (m, 0.03 H), 5.24–5.18 (m, 0.03 H), 2.38 (s, 3 H). **¹³C NMR** (75 MHz, CDCl₃): δ = 137.6 (Cq), 136.5 (Cq), 134.83 (CD), 129.2 (CH), 126.1 (CH), 112.6 (CD₂), 21.2 (CH₃). **²H NMR** (61 MHz, CHCl₃): δ = 6.74 (s, 0.65 D), 5.72 (s, 1 D), 5.22 (s, 1 D). **MS (ESI)**: m/z [M + H]⁺ calcd for C₉H₈D₃: 122.10; found: 122.02 (100%). **MS (ESI)**: m/z [M + H]⁺ calcd for C₉H₉D₂: 121.10; found: 121.18 (63%). **MS (ESI)**: m/z [M + H]⁺ calcd for C₉H₁₀D: 120.10; found: 120.02 (13%). Average deuterium content for *d*-**2j** calculated from the isotopic abundance of MS analyses: 2.49.

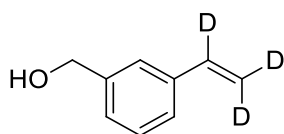
1-Chloro-4-(vinyl-d3)benzene (2k)



Da: 24%, Db > 95%, Dc > 95%

Product **2k** was isolated as a colorless oil (90.9 mg, 65%) using 1-chloro-4-vinylbenzene (138 mg, 1.0 mmol) as the reagent. **¹H NMR** (300 MHz, CDCl₃): δ = 7.45–7.27 (m, 4 H, ref), 6.73–6.66 (m, 0.74 H), 5.78–5.69 (m, 0.03 H), 5.34–5.26 (m, 0.03 H). **¹³C NMR** (75 MHz, CDCl₃): δ = 136.0 (CD), 135.5 (Cq), 133.4 (Cq), 128.7 (CH), 127.5 (CH), 114.4 (CD₂). **²H NMR** (61 MHz, CHCl₃): δ = 6.66 (s, 0.20 D), 5.71 (s, 1 D), 5.25 (s, 1 D). **MS (ESI)**: m/z [M + H]⁺ calcd for C₈H₆D₂Cl: 141.04; found: 141.12 (100%). **MS (ESI)**: m/z [M + H]⁺ calcd for C₈H₅D₃Cl: 142.05; found: 142.13 (41%). Average deuterium content for *d*-**2k** calculated from the isotopic abundance of MS analyses: 2.29

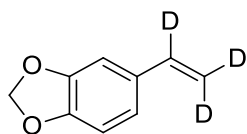
3-(Vinyl-d₃)phenyl]methanol (2m)



Da: 65%, Db>95%, Dc>95%

Product **2m** was isolated as a colorless oil (25.9 mg, 64%) using **1m** (74.4 mg, 0.3 mmol) as the reagent. **¹H NMR** (300 MHz, CDCl₃): δ = 7.44 (s, 1 H), 7.39–7.35 (m, 2 H), 7.30–7.25 (m, 1 H), 6.81–6.65 (m, 0.35 H), 5.81–5.75 (m, 0.04), 5.31–5.25 (m, 0.04 H), 4.70 (s, 2 H, ref), 1.90 (br s, 1 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 141.1 (Cq), 137.8 (CD), 136.5 (Cq), 128.8 (CH), 126.4 (CH), 125.5 (CH), 124.8 (CH), 113.7 (CD₂), 65.2 (CH₂). **²H NMR** (61 MHz, CHCl₃): δ = 6.74 (s, 0.61 D), 5.77 (s, 1 D), 5.26 (s, 1 D). **MS (ESI)**: m/z [M + H]⁺ calcd for C₉H₈D₃O: 138.10; found: 138.18 (100%). **MS (ESI)**: m/z [M + H]⁺ calcd for C₉H₇D₂O: 137.10; found: 137.01 (62%). **MS (ESI)**: m/z [M + H]⁺ calcd for C₉H₉DO: 136.09; found: 136.02 (16%). Average deuterium content for *d*-**2m** calculated from the isotopic abundance of MS analyses: 2.47.

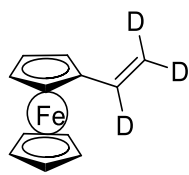
5-(Vinyl-*d*₃)-benzo[d][1,3]dioxole (**2n**)



Da: 17%, Db:80%, Dc: 80%

Product **2n** was isolated as a colorless oil (35.7 mg, 70%) using **1n** (43.9 mg, 0.3 mmol) as the reagent. **¹H NMR** (400 MHz, CDCl₃): δ = 6.96 (s, 1 H, ref), 6.83 (dd, *J* = 8.0, 1.7 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.61 (d, *J* = 2.7 Hz, 0.83 H), 5.96 (s, 2 H), 5.56 (d, *J* = 17.5 Hz, 0.19 H), 5.12 (d, *J* = 10.8 Hz, 0.19 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 148.1 (Cq), 147.5 (Cq), 136.3 (Cq), 132.3 (CD), 121.1 (CH), 112.1 (CD₂), 108.3 (CH), 105.5 (CH), 101.2 (CH₂). **²H NMR** (61 MHz, CHCl₃): δ = 5.60 (s, 0.80 D), 5.15 (s, 0.80 D). **MS (EI)**: *m/z* [M]⁺• calcd for C₉H₅D₃O₂: 151.07; found: 151.13 (12%). **MS (EI)**: *m/z* [M]⁺• calcd for C₉H₆D₂O₂: 150.06; found: 150.12 (86%). **MS (EI)**: *m/z* [M]⁺• calcd for C₉H₇DO₂: 149.06; found: 149.12 (100%). Average deuterium content for *d*-**2n** calculated from the isotopic abundance of MS analyses: 1.56

***d*₃-Vinylferrocene (2o)**



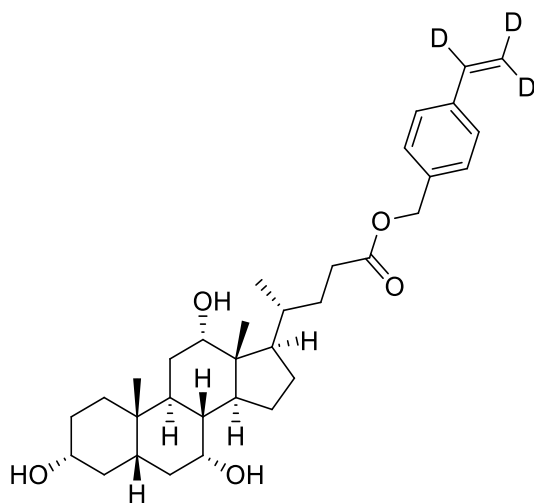
Da: 19%, Db:87%, Dc: 87%

Product **2o** was isolated as a red solid (64.4 mg, 98%) using **1o** (63.9 mg, 0.3 mmol) as the reagent.

¹H NMR (400 MHz, CDCl₃): δ = 6.46–6.42 (m, 0.81 H), 5.33 (d, *J* = 17.5 Hz, 0.13 H), 5.03–5.00 (m, 0.13 H), 4.36 (t, *J* = 1.7 Hz, 2 H, ref), 4.21 (t, *J* = 1.7 Hz, 2 H), 4.11 (s, 5 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 134.5 (CH, CD), 110.7 (CD₂), 83.6 (Cq), 69.2 (5 CH), 68.7 (2 CH), 66.7 (2 CH).

²H NMR (61 MHz, CHCl₃): δ = 5.37 (s, 1 D), 4.99 (s, 1 D). **MS (ESI)**: *m/z* [M]⁺ calcd for C₁₂H₉D₃Fe: 215.05; found: 215.32 (24%). **MS (ESI)**: *m/z* [M]⁺ calcd for C₁₂H₁₀D₂Fe: 214.04; found: 214.32 (100%). Average deuterium content for *d*-**2o** calculated from the isotopic abundance of MS analyses: 2.20

E-4-(Vinyl-d₃)benzyl 4-[(3R,5S,7R,8R,9S,10S,12S,13R,14S,17R)-3,7,12-Trihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-17-yl]pentanoate (2p)

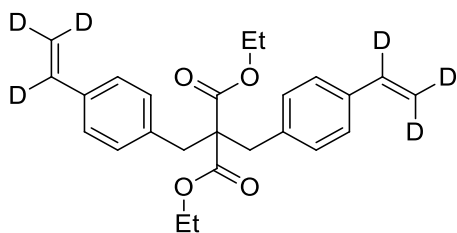


2p, 64%

Da: 92%, Db > 95%, Dc > 95%

Product **2p** was isolated as a white solid (101 mg, 64%) using **1p** (157 mg, 0.3 mmol) as the reagent. **¹H NMR** (400 MHz, CDCl₃): δ = 7.39 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.2 Hz, 2 H, ref), 6.71–6.68 (m, 0.08 H), 5.74–5.71 (m, 0.01 H), 5.25–5.22 (m, 0.01 H), 5.13–5.04 (m, 2 H), 3.95 (t, *J* = 3.0 Hz, 1 H), 3.84 (q, *J* = 3.0 Hz, 1 H), 3.48–3.41 (m, 1 H), 2.44–2.14 (m, 7 H), 1.96–1.21 (m, 18 H), 1.13–1.03 (m, 1 H), 1.00–0.91 (m, 4 H), 0.88 (s, 3 H), 0.65 (s, 3 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 174.3 (Cq), 137.5 (Cq), 136.2 (CH, CD), 135.6 (Cq), 128.6 (2 CH), 126.4 (2 CH), 113.7 (CD₂), 73.2 (CH), 72.0 (CH), 68.5 (CH), 65.9 (CH₂), 47.1 (CH), 41.7 (CH), 41.5 (CH), 39.5 (CH, CH₂), 35.4 (CH₂), 35.3 (CH), 34.9 (CH₂), 34.8 (Cq), 31.4 (CH₂), 31.0 (CH₂), 30.5 (CH₂), 28.2 (CH₂), 27.6 (CH₂), 26.4 (CH), 23.3 (CH₂), 22.5 (CH₃), 17.4 (CH₃), 14.3 (Cq), 12.5 (CH₃). **²H NMR** (61 MHz, CHCl₃): δ = 6.77 (0.95 D), 5.73 (1 D), 5.25 (0.72 D). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₃₃H₄₅D₃NaO₅: 550.36; found: 550.12 (100%). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₃₃H₄₆D₂NaO₅: 549.36; found: 549.20 (32%). Average deuterium content for *d*-**2p** calculated from the isotopic abundance of MS analyses: 2.76.

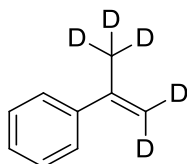
Diethyl 2,2-Bis[4-(vinyl-*d*₃)benzyl]malonate (2q)



Da:22%, Db > 95%, Dc > 95%

Product **2q** was isolated as a viscous oil (31.9 mg, 60%) using **1q** (53 mg, 0.14 mmol) as the reagent. **¹H NMR** (400 MHz, CDCl₃): δ = 7.32 (d, *J* = 7.9 Hz, 4 H), 7.16 (d, *J* = 7.9 Hz, 4 H), 6.70 (s, 1.56 H), 5.76–5.73 (m, 0.06 H), 5.25–5.22 (m, 0.06 H), 4.15 (q, *J* = 7.1 Hz, 4 H), 3.24 (s, 4 H, ref), 1.20 (t, *J* = 7.1 Hz, 6 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 170.9 (Cq), 136.3 (CH, CD), 136.2 (Cq), 136.0 (Cq), 130.3 (CH), 126.1 (CH), 113.2 (CD₂), 61.3 (CH₂), 60.1 (Cq), 38.9 (CH₂), 13.9 (CH₃). **²H NMR** (61 MHz, CHCl₃): δ = 6.74 (s, 0.25 D), 5.75 (s, 1 D), 5.26 (s, 1 D). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₂₅H₂₄D₄NaO₄: 419.21; found: 419.27 (100%). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₂₅H₂₅D₃NaO₄: 418.21; found: 418.11 (47%). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₂₅H₂₃D₅NaO₄: 420.22; found: 420.18 (39%). Average deuterium content for *d*-**2q** calculated from the isotopic abundance of MS analyses: 3.75.

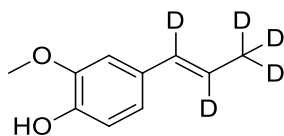
(Prop-1-en-2-yl-*d*₅)benzene (2r)



CD₃:92%, Db > 93%, Dc > 93%

Product **2r** was isolated as a colorless oil (68.5 mg, 56%) using *a*-methylstyrene (118 mg, 1.0 mmol) as the reagent. **¹H NMR** (300 MHz, CDCl₃): δ = 7.58–7.45 (m, 2 H, ref), 7.45–7.23 (m, 3 H), 5.40–5.38 (m, 0.07 H), 5.12–5.09 (m, 0.07 H), 2.24–2.13 (m, 0.24 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 143.0 (Cq), 141.2 (Cq), 128.2 (CH), 127.4 (CH), 125.5 (CH), 111.9 (CD₂), 21.5 (CD₃). **²H NMR** (61 MHz, CHCl₃): δ = 5.40 (s, 1 D), 5.13 (s, 1 D), 2.13 (s, 2.78 D). **MS (ESI)**: *m/z* [M + H]⁺ calcd for C₉H₆D₅: 124.12; found: 124.02 (100%). **MS (ESI)**: *m/z* [M + H]⁺ calcd for C₉H₇D₄: 123.11; found: 123.05 (44%). **MS (ESI)**: *m/z* [M + H]⁺ calcd for C₉H₈D₃: 122.10; found: 122.00 (18%). Average deuterium content for *d*-**2r** calculated from the isotopic abundance of MS analyses: 4.50.

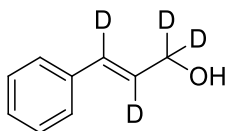
*d*₅-Isoeugenol (**2s**)



Da: 20%, CD₃: 12%, Dc:92%

Product **2s** was isolated as a pale yellow oil (150 mg, 90%) using isoeugenol (164 mg, 1 mmol) as the reagent. ¹H NMR (400 MHz, CDCl₃): δ = 6.94–6.77 (m, 3 H), 6.31 (s, 0.79 H), 6.09 (s, 0.08 H), 5.55 (s, 0.82 H, OH), 3.90 (s, 3 H, ref), 1.91–1.79 (m, 2.65 H). ¹³C NMR (101 MHz, CDCl₃): δ = 146.67 (Cq), 144.8 (Cq), 130.7 (CH), 129.6 (Cq), 123.5 (CD), 119.4 (CH), 114.5 (CH, CD weak), 108.0 (CH), 56.0 (OCH₃), 18.4 (CH₃, CD₃ weak). ²H NMR (61 MHz, CHCl₃): δ = 6.11 (s, 1 D), 1.79 (s, 0.11 D). MS (EI): m/z [M]⁺• calcd for C₁₀H₈D₄O₂: 168.11; found: 168.14 (1%). MS (EI): m/z [M]⁺• calcd for C₁₀H₉D₃O₂: 167.10; found: 167.15 (3%). MS (EI): m/z [M]⁺• calcd for C₁₀H₁₀D₂O₂: 166.10; found: 166.15 (18%). MS (EI): m/z [M]⁺• calcd for C₁₀H₁₁DO₂: 165.09; found: 165.15 (100%). Average deuterium content for *d*-**2s** calculated from the isotopic abundance of MS analyses: 1.23.

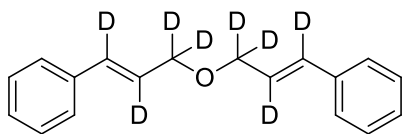
*d*_n-(*E*)-3-Phenylprop-2-en-1-ol (**2t**)



Da: 12%, CD₂ > 13%, Dc < 5%

Product **2t** was isolated as a yellow oil (27.4 mg, 20%) using **1u** (134 mg, 1 mmol) as the reagent. ¹H NMR (400 MHz, CDCl₃): δ = 7.42–7.36 (m, 2 H, ref), 7.35–7.28 (m, 2 H), 7.28–7.21 (m, 1 H), 6.65–6.58 (m, 0.40 H), 6.42–6.32 (m, 1.97 H), 4.33 (dd, *J* = 5.7, 1.5 Hz, 0.74 H). ¹³C NMR (101 MHz, CDCl₃): δ = 136.67, 136.60 (Cq), 131.2 (CH, CD), 128.6 (2 CH), 128.5 (CH, CD), 127.7 (CH), 126.5 (2 CH), 63.8 (CH₂). ²H NMR (61 MHz, CHCl₃): δ = 6.66 (0.60 D), 4.41 (1.17 D). MS (EI): m/z [M]⁺• calcd for C₉H₇D₃O: 137.09; found: 137.09 (100%). MS (EI): m/z [M]⁺• calcd for C₉H₈D₂O: 136.09; found: 136.08 (33%). MS (EI): m/z [M]⁺• calcd for C₉H₉DO: 135.08; found: 135.07 (13%). MS (EI): m/z [M]⁺• calcd for C₉H₁₀O: 134.07; found: 134.06 (52%). Average deuterium content for *d*-**2t** calculated from the isotopic abundance of MS analyses: 1.78.

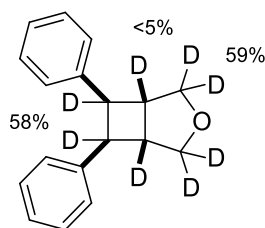
***d_n*-[(1E,1'E)-Oxybis(prop-1-ene-3,1-diyl)]dibenzene (3t)**



Da: 10%, CD₂: 10%, Dc < 5%

Product **3t** was isolated as yellow oil (58.8 mg, 46%) using **1u** (134 mg, 1 mmol) as the reagent. **¹H NMR** (400 MHz, CDCl₃): δ = 7.48–7.38 (m, 4 H, ref), 7.36–7.28 (m, 4 H), 7.27–7.19 (m, 2 H), 6.67 (d, *J* = 16.0 Hz, 0.82 H), 6.41–6.30 (m, 1.94 H), 4.24 (dd, *J* = 6.1, 1.4 Hz, 1.54 H). **¹³C NMR** (101 MHz, CDCl₃): d = 136.71, 136.64 (Cq), 132.64, 132.61 (CH, CD), 128.6 (2 CH), 127.7 (CH), 126.53, 126.51 (2CH), 126.03, 126.00, 125.77, 125.75 (CH, CD), 70.8, 70.7 (CH₂, CHD). **²H NMR** (61 MHz, CHCl₃): d = 6.67 (0.60 D), 4.22 (1.38 D). MS analyses on **3t** (ESI, EI) were unsuccessful.

***d_n*-6,7-Diphenyl-3-oxabicyclo[3.2.0]heptane (4t)**



Ir[dF(CF₃)ppy]₂(dtbbpy)(PF₆) (1.79 mg, 0.0016 mmol) was added to a Schlenk tube containing a degassed solution of **3t** (40 mg, 0.16 mmol) in DMF (16 mL). The homogeneous solution was irradiated with white LED strips for 16 h. The mixture was then diluted with Et₂O (30 mL) and H₂O (5 mL). The aqueous layer was separated and extracted with Et₂O (2 × 30 mL). The combined organic layers were washed with water (2 × 5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (n-hexane/EtOAc, 95:5) yielding **4t** (23.4 mg, 58%) as a pale yellow solid. M. p.: 86–87 °C. **¹H NMR** (400 MHz, CDCl₃): δ = 7.12–7.05 (m, 4 H), 6.92–7.03 (m, 6 H, ref), 4.11 (dd, *J* = 9.5, 1.6 Hz, 0.83 H), 3.79–3.68 (m, 1.70 H), 3.35–3.27 (m, 1.96 H). **¹³C NMR** (101 MHz, CDCl₃): δ = 140.81, 140.78 (Cq), 128.1 (CH), 127.7 (CH), 125.6 (CH), 74.04, 74.00 (CH₂, CHD), 47.20, 47.07 (CH, CD), 42.14, 42.10, 41.84, 41.80 (CH, CD). **²H NMR** (61 MHz, CHCl₃): δ = 4.08 (1.17 D), 3.72 (2.51 D). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₁₈H₁₂D₆NaO: 279.16; found: 279.05 (100%). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₁₈H₁₃D₅NaO: 278.16; found 278.10 (8%). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₁₈H₁₄D₄NaO: 277.15; found 277.08 (15%). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₁₈H₁₅D₃NaO: 276.14; found 276.10 (8%). **MS (ESI)**: *m/z* [M + Na]⁺ calcd for C₁₈H₁₆D₂NaO: 275.14; found 275.10 (39%). Average deuterium content for *d*-**4t** calculated from the isotopic abundance of MS analyses: 4.66.

CHAPTER 4

Inter/Intramolecular Cascade of 1,6-Enynes Catalyzed by All-Metal Aromatic Tripalladium Complexes and Carboxylic Acids

Introduction

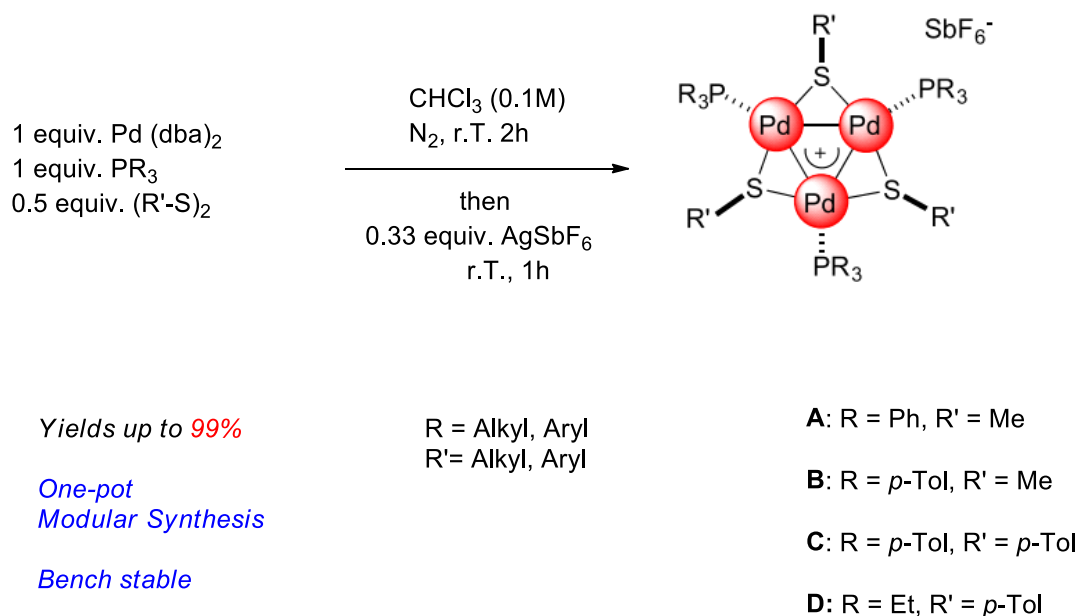
The concept of aromaticity is referred to those compounds having planar or quasiplanar cyclic conjugated structures according to Hückel's rule of $(4n + 2) \pi$ electrons. This bonding theory was introduced by Kekulé after definitive identification of the structure of benzene. This achievement generated so much excitement that many compounds featuring benzene as core have been widely used during last century for many purposes, from material science to medicine, arousing significant social impact.⁴⁸

Delocalized molecular orbitals can be found in structures featuring transition metals too. One of those are metallaromatic compounds in which transition metal *d*-orbitals are involved in delocalized molecular orbitals.⁴⁹

Although the absence of versatile methods for the synthesis of these compounds does not allow their widespread use, many examples of these fascinating compounds such as palladium, platinum, ruthenium trinuclear clusters have been reported in the literature.^{50,51,52} In these clusters metals exist in their oxidation state +4/3 and the complex HOMO resulted from the combination of *d*-atomic orbitals of the three metals. Furthermore *d*-atomic orbitals produce two LUMOs whose energetic level was reduced by the positive charge of the complex.

These complex can be prepared by commercially available phosphines, disulfides and zero valent Pd or Pt. Utilization of phosphine and disulfides allows modulation of the steric and electronic effects and the final product is stable to oxygen and moisture (Scheme 1).

Our interest in the reactivity of these complex allowed us to study their catalytic properties. Internal alkynes can be converted into *Z*-alkenes by employing low loading (down to 0.01%) of trinuclear palladium cluster (Figure 1, a). Furthermore we can employ tripalladium complexes for catalyzing Suzuki and Kumada reactions (Figure 1, b-c).⁶¹⁻⁶² These chemical transformations derived from the alkynophilicity properties of this complex and our intention was to extend this reactivity to C-C bond forming reactions, too. Cycloisomerizations promoted by palladium, gold and platinum complexes are well known in the literature.⁵³⁻⁶⁰



Scheme 1. Synthesis of Trinuclear all-metal aromatic Palladium clusters

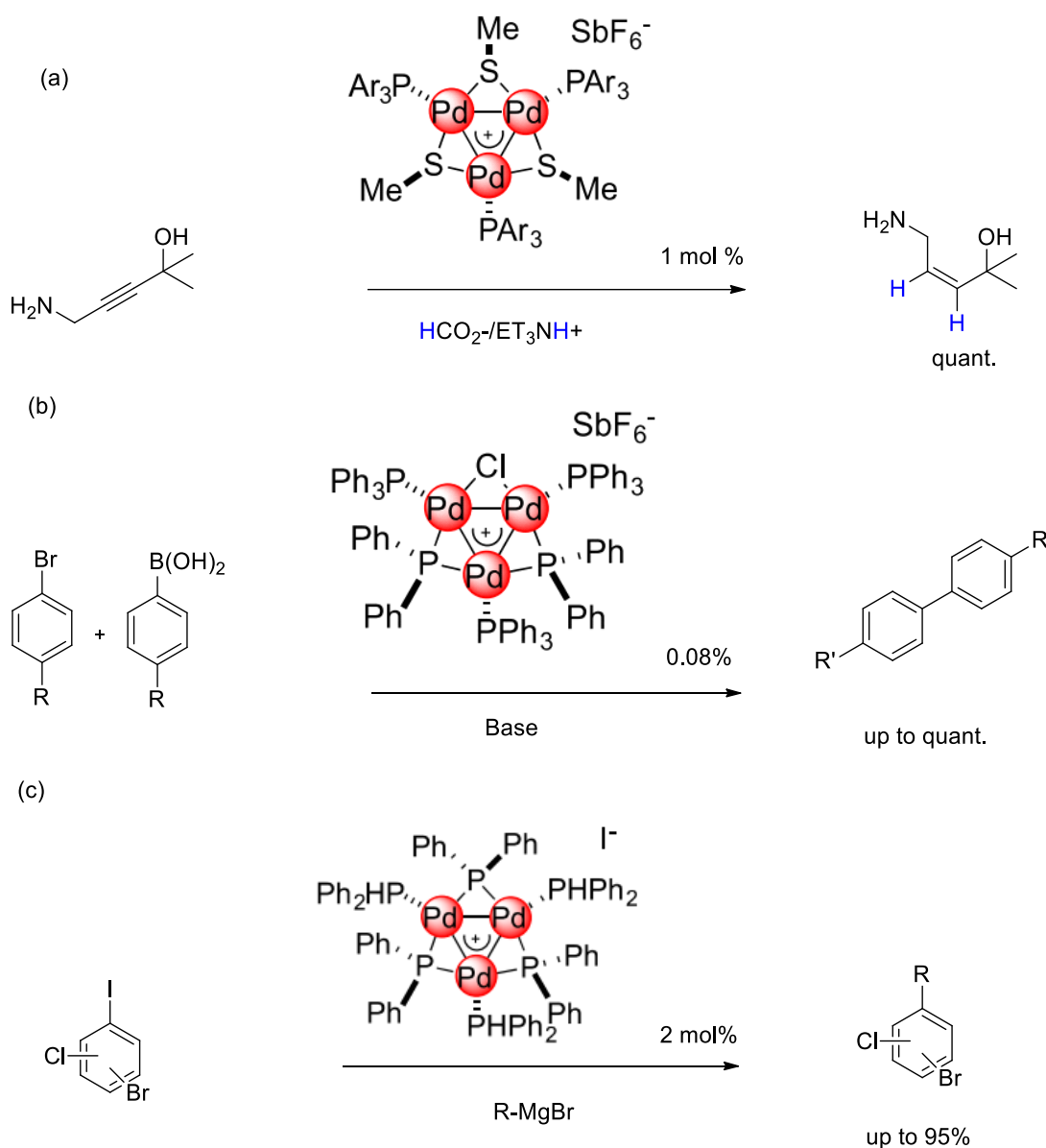


Figure 1. Catalytic Applications of Aromatic Pd_3^+ Complexes

- ⁴⁸ Martín, N.; Scott, L. T. *Challenges in Aromaticity: 150 Years after Kekulé's Benzene*. *Chem. Soc. Rev.* **2015**, 44, 6397.
- ⁴⁹ Frogley, B. J.; Wright, L. J. *Recent Advances in Metallaaromatic Chemistry*. *Chem. - Eur. J.* **2018**, 24, 2025.
- ⁵⁰ Blanchard, S.; Fensterbank, L.; Gontard, G.; Lacôte, E.; Maestri, G.; Malacria, M. *Synthesis of Triangular Tripalladium Cations as Noble-Metal Analogues of the Cyclopropenyl Cation*. *Angew. Chem., Int. Ed.* **2014**, 53, 1987.
- ⁵¹ Wang, Y.; Monfredini, A.; Deyris, P.-A.; Blanchard, F.; Derat, E.; Maestri, G.; Malacria, M. *All-Metal Aromatic Cationic Palladium Triangles Can Mimic Aromatic Donor Ligands with Lewis Acidic Cations*. *Chem. Sci.* **2017**, 8, 7394.
- ⁵² Kulichenko, M.; Fedik, N.; Monfredini, A.; Munoz-Castro, A.; Balestri, D.; Boldyrev, A. I.; Maestri, G. "Bottled" spiro-doubly aromatic trinuclear $[\text{Pd}_2\text{Ru}]^+$ complexes. *Chem. Sci.* **2021**, 12, 477.
- ⁵³ Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Cycloisomerization of 1,n-Enynes: Challenging Metal-Catalyzed Rearrangements and Mechanistic Insights*. *Angew. Chem., Int. Ed.* **2008**, 47, 4268.
- ⁵⁴ Aubert, C.; Buisine, O.; Malacria, M. *The Behavior of 1, n -Enynes in the Presence of Transition Metals*. *Chem. Rev.* **2002**, 102, 813.
- ⁵⁵ Hu, Y.; Bai, M.; Yang, Y.; Zhou, Q. *Metal-Catalyzed Enyne Cycloisomerization in Natural Product Total Synthesis*. *Org. Chem. Front.* **2017**, 4, 2256.
- ⁵⁶ Stathakis, C. I.; Gkizis, P. L.; Zografos, A. L. *Metal-Catalyzed Cycloisomerization as a Powerful Tool in the Synthesis of Complex Sesquiterpenoids*. *Nat. Prod. Rep.* **2016**, 33, 1093.
- ⁵⁷ Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J.; Thomas, A. P. *The Palladium-Catalyzed Enyne Cycloisomerization Reaction in a General Approach to the Asymmetric Syntheses of the PicROTOXANE Sesquiterpenes. Part I. First-Generation Total Synthesis of Corianin and Formal Syntheses of PicROTOXININ and PicROTOIN*. *J. Am. Chem. Soc.* **1999**, 121, 6183.
- ⁵⁸ Dufert, A.; Werz, D. B. *Carbopalladation Cascades Using Carbon-Carbon Triple Bonds: Recent*

Advances to Access Complex Scaffolds. Chem. - Eur. J. **2016**, 22, 16718. ⁵⁹Fürstner, A.; Stelzer, F.; Szillat, H. *Platinum-Catalyzed Cycloisomerization Reactions of Enynes. J. Am. Chem. Soc.* **2001**, 123, 11863. ⁶⁰Jiménez-Núñez, E.; Echavarren, A. M. *Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective. Chem. Rev.* **2008**, 108, 3326. ⁶¹Fu, F.; Xiang, J.; Cheng, H.; Cheng, L.; Chong, H.; Wang, S.; Li, P.; Wei, S.; Zhu, M.; Li, Y. *A Robust and Efficient Pd₃ Cluster Catalyst for the Suzuki Reaction and Its Odd Mechanism. ACS Catal.* **2017**, 7, 1860. ⁶²Diehl, C. J.; Scattolin, T.; Englert, U.; Schoenebeck, F. *C–I Selective Cross-Coupling Enabled by a Cationic Palladium Trimer. Angew. Chem., Int. Ed.* **2019**, 58, 211

Results and discussions

1a was used as substrate for optimizing reaction conditions. The reaction was performed in toluene at reflux under N₂ conditions. In the presence of the complex **A** (1 mol %) and benzoic acid (1 equiv.) **1a** delivered the tricycle **2a** in 45% as a single regioisomer. Other palladium catalysts such as Pd(OAc)₂, Pd(PPh₃)₄ and Pd₂(dba)₃ (10% mol) were ineffective. With the conditions in hand, we extend this method to a variety of enyne in order to deliver their corresponding spirocycles (Figure 2)

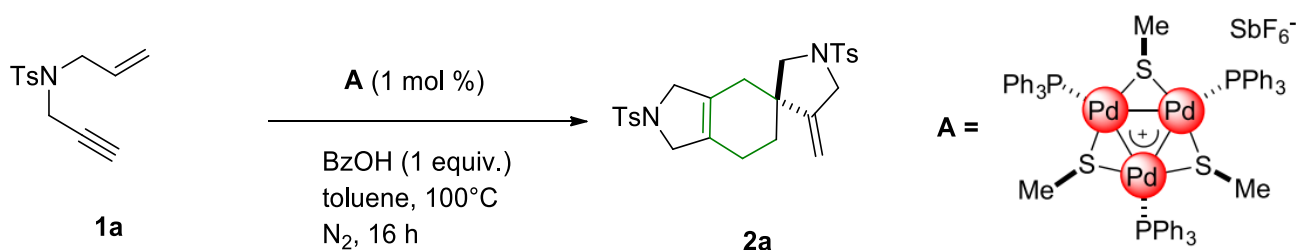
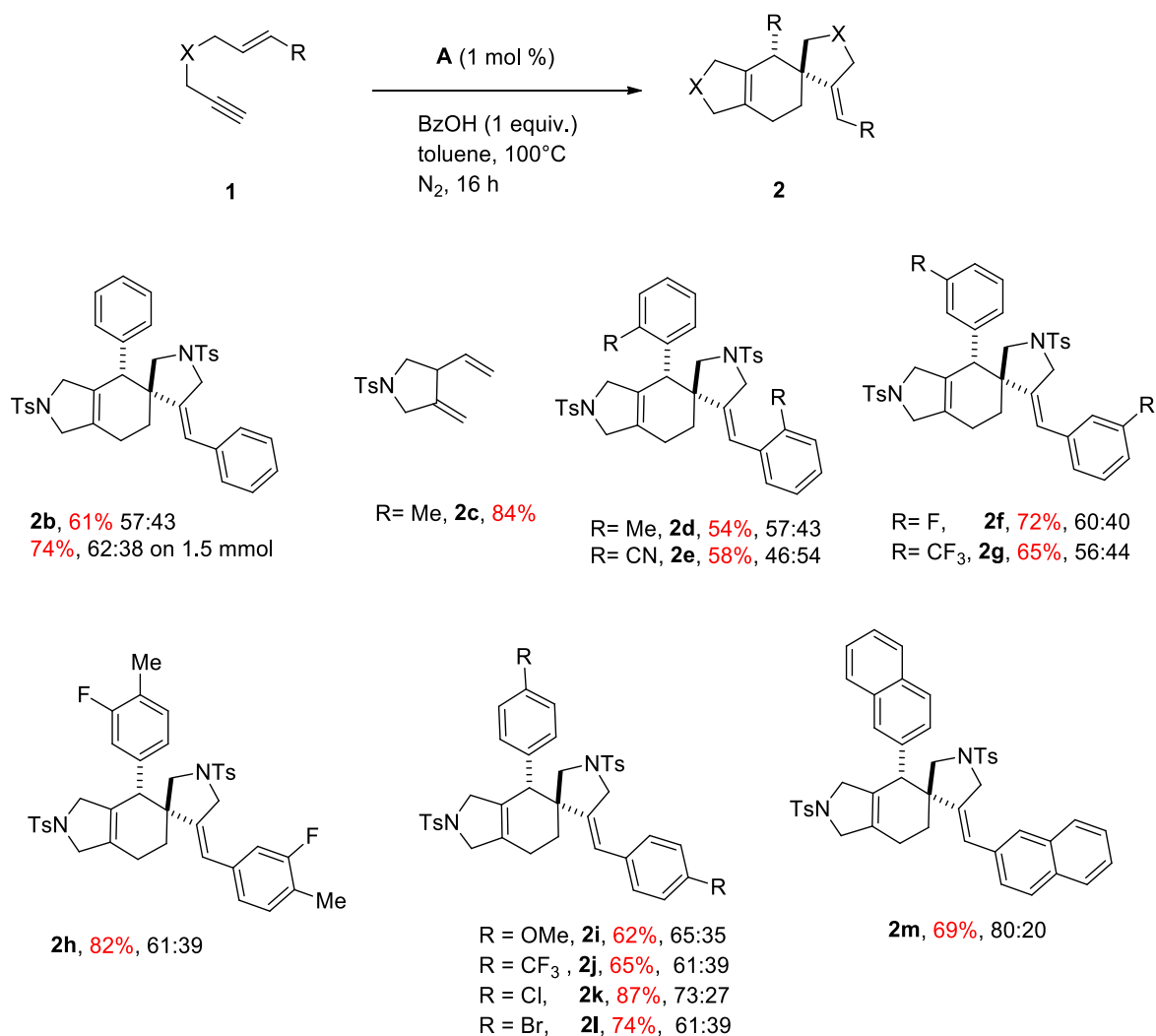


Figure 1. Reaction between **1a** and complex **A**



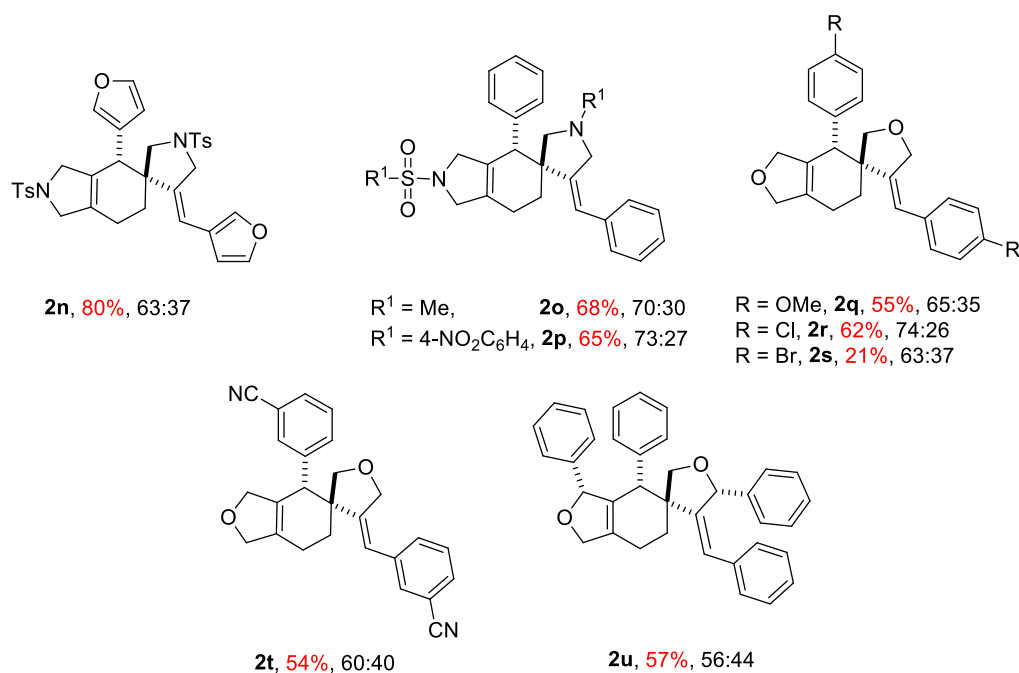


Figure 2. Scope of the intermolecular cascade of 1,6-enynes catalyzed by trinuclear all-metal aromatic palladium cluster A

Installation of phenyl group into the vinyl group proved advantageous for the reaction. The product **2b** was isolated in moderate yield and diastereoselectivity (61%, 57:43 dr). The reaction was scale-up to 1.5 mmol, delivering the product in higher yield (74%) and better diastereoselectivity (62:38). Diastereoselectivity was calculated thorough ¹HNMR by comparing the integrals of the signals of each isomers. Interestingly substrate **1c**, bearing a methyl group in its double bond, afforded its corresponding 1,4 diene in 84%. This result suggested that **2c** was delivered after insertion of the alkyne moiety to the Pd-H and after a β-hydrogen elimination had occurred (See Scheme 9 for reaction mechanism). Methyl and cyano groups in *ortho* positions to vinyl group in substrates **1d** and **1e** allowed moderate isolation of the corresponding products (54% and 58%, respectively). Electron-withdrawing groups did not influence the outcome of the reaction (72% for **2f**, 65% for **2g** and 82% for **2h**). That was also confirmed by **2i** and **2j** in which a methyl and -CF₃ at the same position allowed the isolation of their corresponding spirocycles in similar yield (62% and 65% respectively) and diastereoselectivity. Surprisingly **1k** and **1l** proved highly reactive, delivering their tricycles in 87% and 74%. These two results were surprising because aryl chlorides and bromides generally are not tolerated by low valent mononuclear palladium species. Bulkier groups such as 2-naphthyl group (substrate **1m**) improved diastereoselectivity (69%, 80:20 dr). The reaction is tolerant to heterocycles such as furans (**2n**, 80%, 63:37 dr). Different sulfonyl groups into the tether such as mesyl and *para*-nitrosulfonyl allowed the formation of **2o** and **2p** in similar yield (68% and 65%, respectively) and diastereoselectivity (70:30 and 73:27 respectively). Further extension of this catalytic approach was accomplished by O-tether enynes. A bromide group in the *para* position of the vinyl group proved detrimental for the formation of product **2s** (21%, 63:37 dr). Isolation of **2t** was similar to its corresponding N-tether spirocycle **2e** (54%, 60:40 dr). Introduction of a phenyl group at the propargyl moiety in substrate **1u** enables the formation of the cycle **2u** in 57%. Preparation of substrate **1u** prompted us to study a synthetic method for making Ramonanines.⁷⁸ However this strategy did not work properly because catalyst decomposition occurred. Configuration of each isomers was determined by COSY, HSQC and HMBC.

Then we moved to the synthesis of isotopic labelled compounds employing substrate (D)-**1b** in the presence of deuterated benzoic acid (Figure 3). Its corresponding tricycle was provided in 77%. ^1H NMR and ^2D NMR spectra showed the incorporation of deuterium into the desired product and revealed unselective labelling on several positions into the cyclohexene moiety. Moreover electron spray ionization mass spectrometer (ESI-MS) gave us more informations regarding the abundancy of products obtained. The most abundant was a trideuterated product (D)₃-**2b** (37%, Figure 3) compared to the bi- and tetradeuterated ones ((D)₂-**2b** and (D)₄-**2b**, respectively). These results allowed us to assume that during the catalytic process a deuterium transfer from BzOD to the enyne occurs. Afterwards (D)-**1b** gave back an hydrogen atom to the resulting benzoate specie, probably from the β -position of the styryl arm. The lower yield of tetradeuterated product was probably due to the accumulation of the resulting protio benzoic acid in solution.

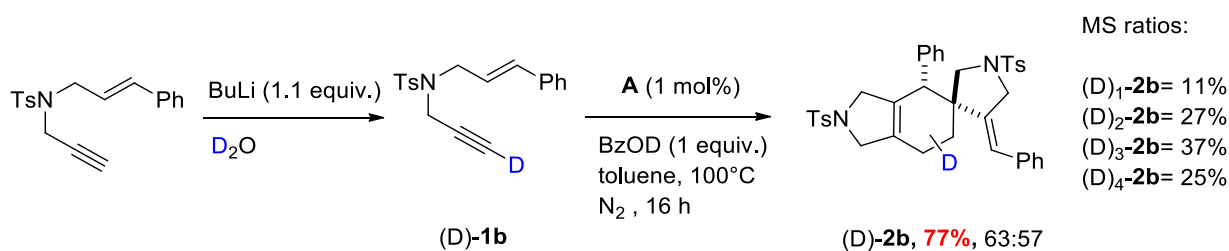


Figure 3. Synthesis of labelled spirocycle (D)-**2b**

Enyne **1v**, obtained by reduction of its corresponding 1,3 dicarbonyl one with DIBAL-H, did not afford the desired product. Conversely we observed the formation of acetal **2'v** in 42% (Figure 4).⁷⁴

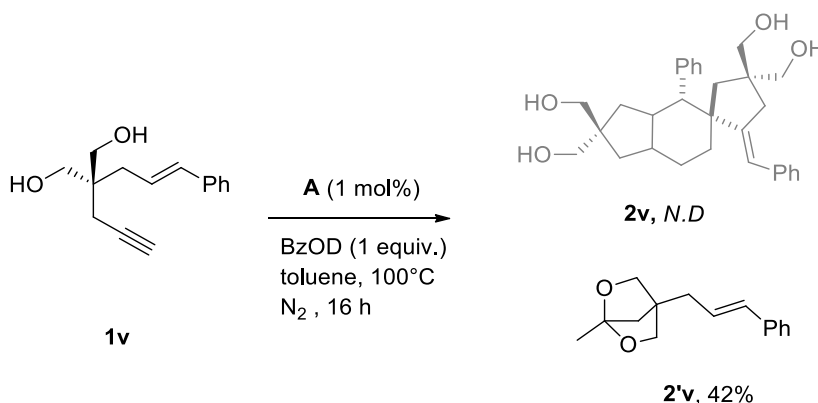
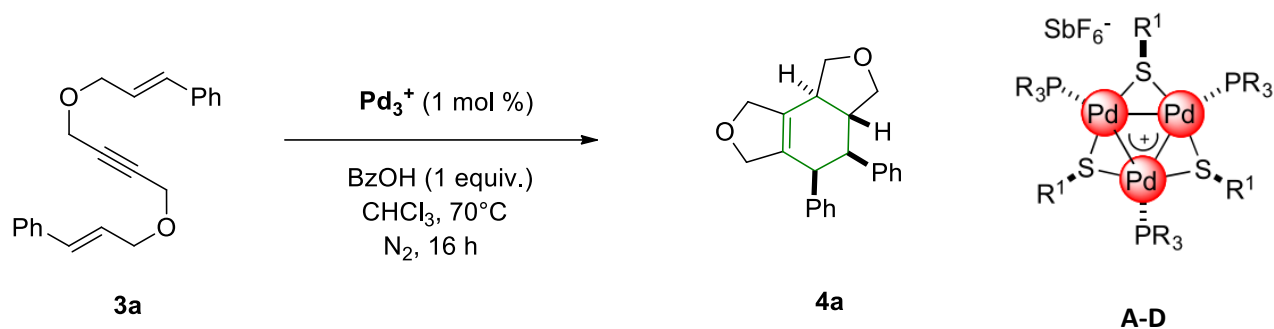


Figure 4. Synthesis of Bicyclic Acetal **2'v**

Afterwards we synthesized dienyne **3a** with the intention of studying its reactivity in the presence of palladium clusters (Scheme 2). We started our investigation analyzing the reaction conditions. **3a** was used as reactant and other clusters of palladium were prepared and tested. In the presence of catalyst **A**, chloroform as solvent at 70°C the desired product **4a** was recovered in 88% as a single regioisomer. The reaction can be performed at 45°C. Similar results were achieved even employing clusters **B** and **C** (80% and 81% respectively). On the other hand cluster **D** proved detrimental. This complex had an electro- donating group, demonstrating that it has a negative impact on the reaction and suggesting that alkyne reacts with the complex after replacing a phosphine from the catalyst. Relative configuration of product **4** was established by a HSQC spectrum.



entry	Pd_3^+	R	R ¹	Yields (%)
1	A	C ₆ H ₅	Me	88
2	B	4-MeC ₆ H ₄	Me	80
3	C	4-MeC ₆ H ₄	4-MeC ₆ H ₄	81
4	D	Et	C ₇ H ₇	36

Scheme 2. Optimization of reaction conditions with dyene **3a**

With the conditions in hands we extended the feasibility of this method to a variety of dienynes. On average all dienynes **3a-f** afforded their corresponding cycles in good yield with remarkable diastereoselectivity (Figure 5). Interestingly, substrate **3f** provided a mixture of two regioisomers isolated in 1:1 ratio (85%), both obtained with excellent diastereocontrol (97:3). Finally we tested enyne **3g** bearing one *cis*- and one *trans*- beta-styryl arm (Figure 6). The experiment was set-up to understand the behaviour of the two different alkene moieties. The reaction provided a mixture of products **4a/4g** in 38:62 ratio (39% total yield). It seemed that substrate **3g** might provide two monocyclic 1,3-dienes (**X** and **Y**) in their *E,E*- form. Whereas monocycle **X** would deliver **4a**, intermediate **Y** would afford **4g** which has on the contrary both phenyl groups in an *anti*-arrangement. We also isolated the *Z,E*- diene **4g'''** in 19%, which is likely unable to evolve into products **4g'** and **4g**.

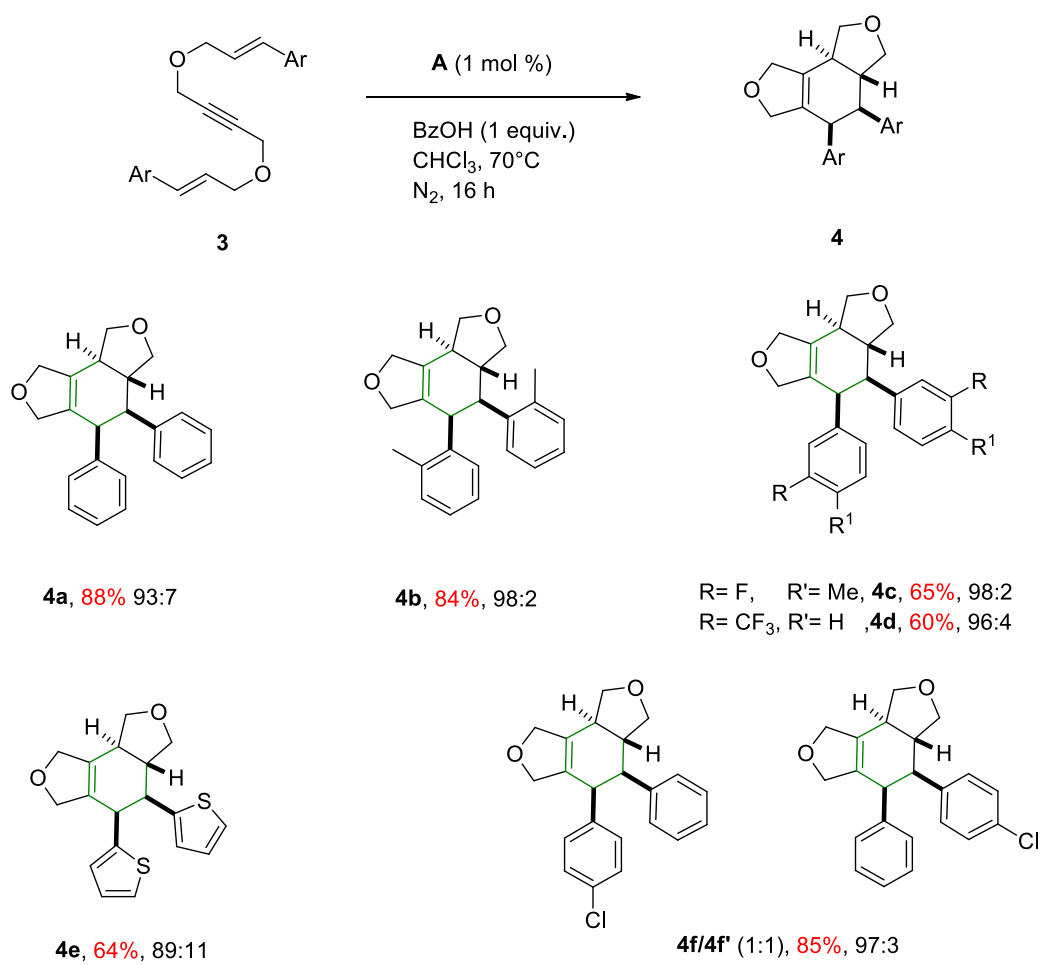


Figure 5. Intramolecular Cascade of Dienynes **3**

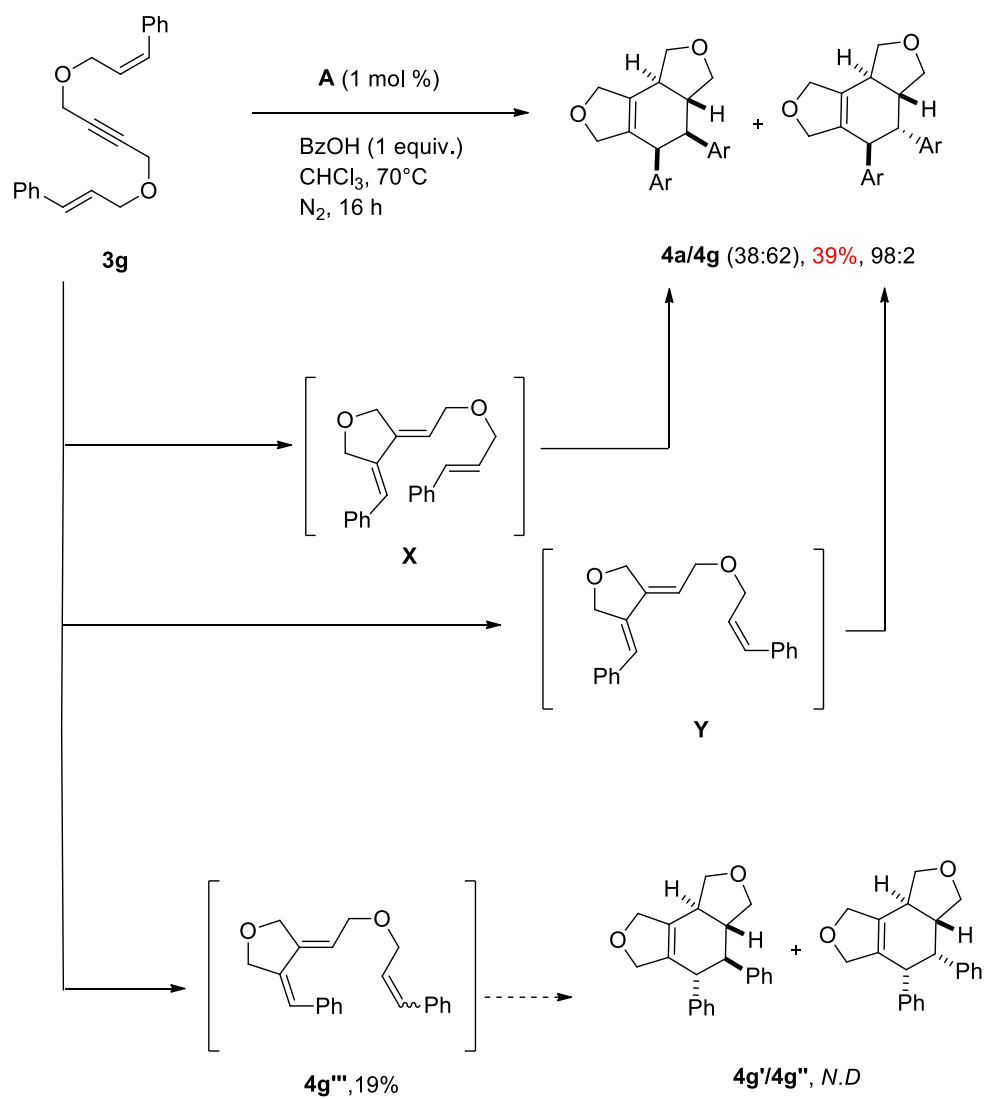


Figure 6. Cyclization of Dienynes **3g**

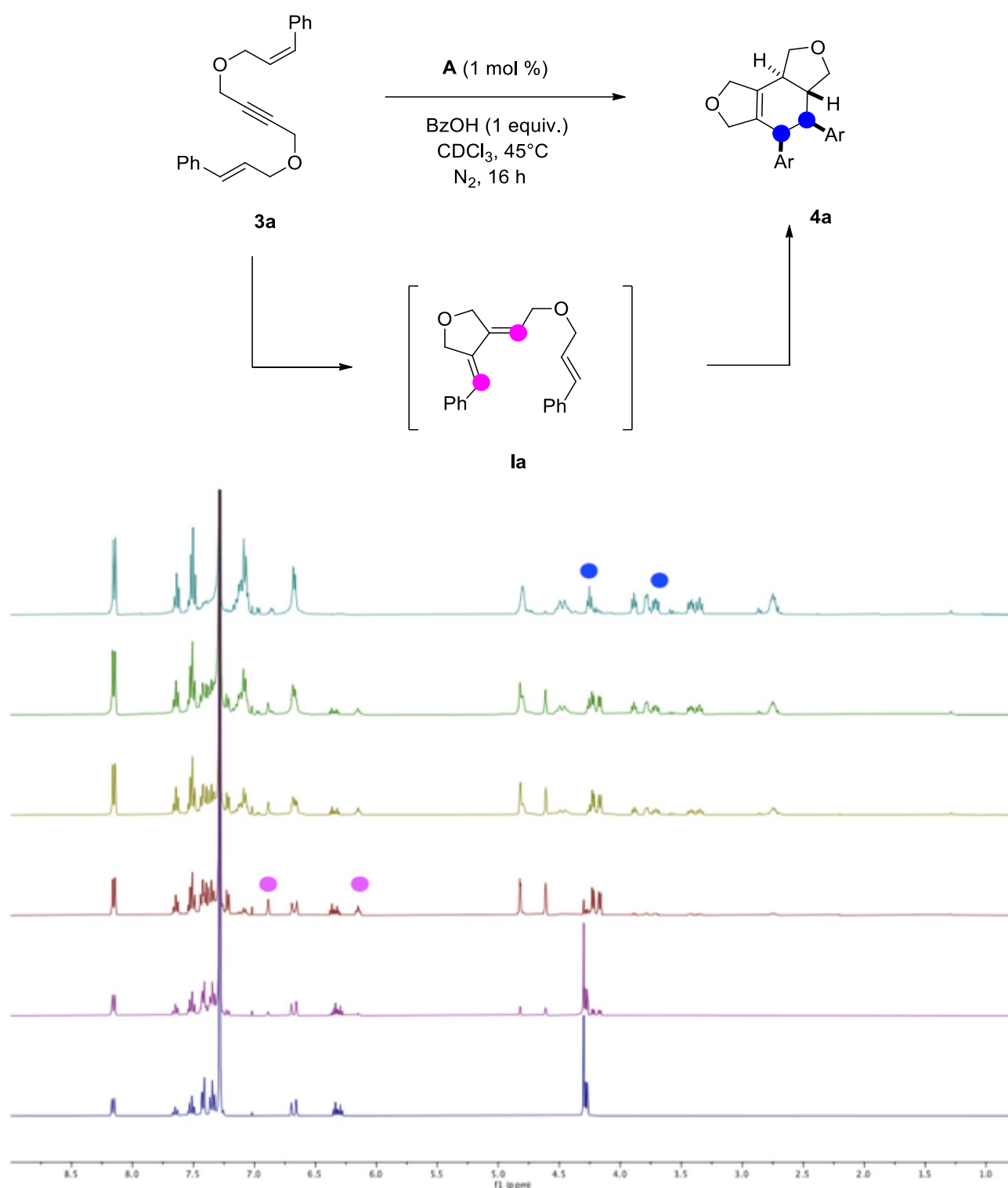


Figure 7. ¹H NMR analyses on the cyclization of **3a**.

We monitored reaction of **3a** in CDCl₃ through ¹H NMR (Figure 7). After one hour, in presence of benzoic acid (1 equiv.) and complex **A**, **1a** started to appear and reached its highest concentration after 3 hours. At this point no signals related to **4a** were detected. After 10 hours traces **4a** started to show up and it becomes the main specie after 16 hours. These results seems to establish that the alkyne moiety and one of two vinyl arms of **3a** are involved in the first cycloisomerization.

In order to demonstrate that Palladium complex **A** participates during intramolecular cyclization we monitored the reaction of **3a** through ^{31}P NMR (Figure 8). The peak of Pd cluster is at 16 ppm (in red). After 1 hour this peak disappeared and another one comes up at 27 ppm (peak in blue). This peak would likely indicate the presence of a catalytically active adduct. It persisted for 10 hours. After 10 hours Pd cluster peak rose again (peak in red). At this moment, the diyne was completely consumed and both **4a** and intermediate **Ia** (see Figure 8) are in the crude. After other 6 hours **4a** is the most abundant specie in solution and the peak of Pd cluster is much higher than other adduct. This result confirmed that Pd cluster is involved during the intramolecular Diels Alder and demonstrated the regeneration of the complex at the end of the reaction. Attempts to isolate the specie indicated in blue failed.

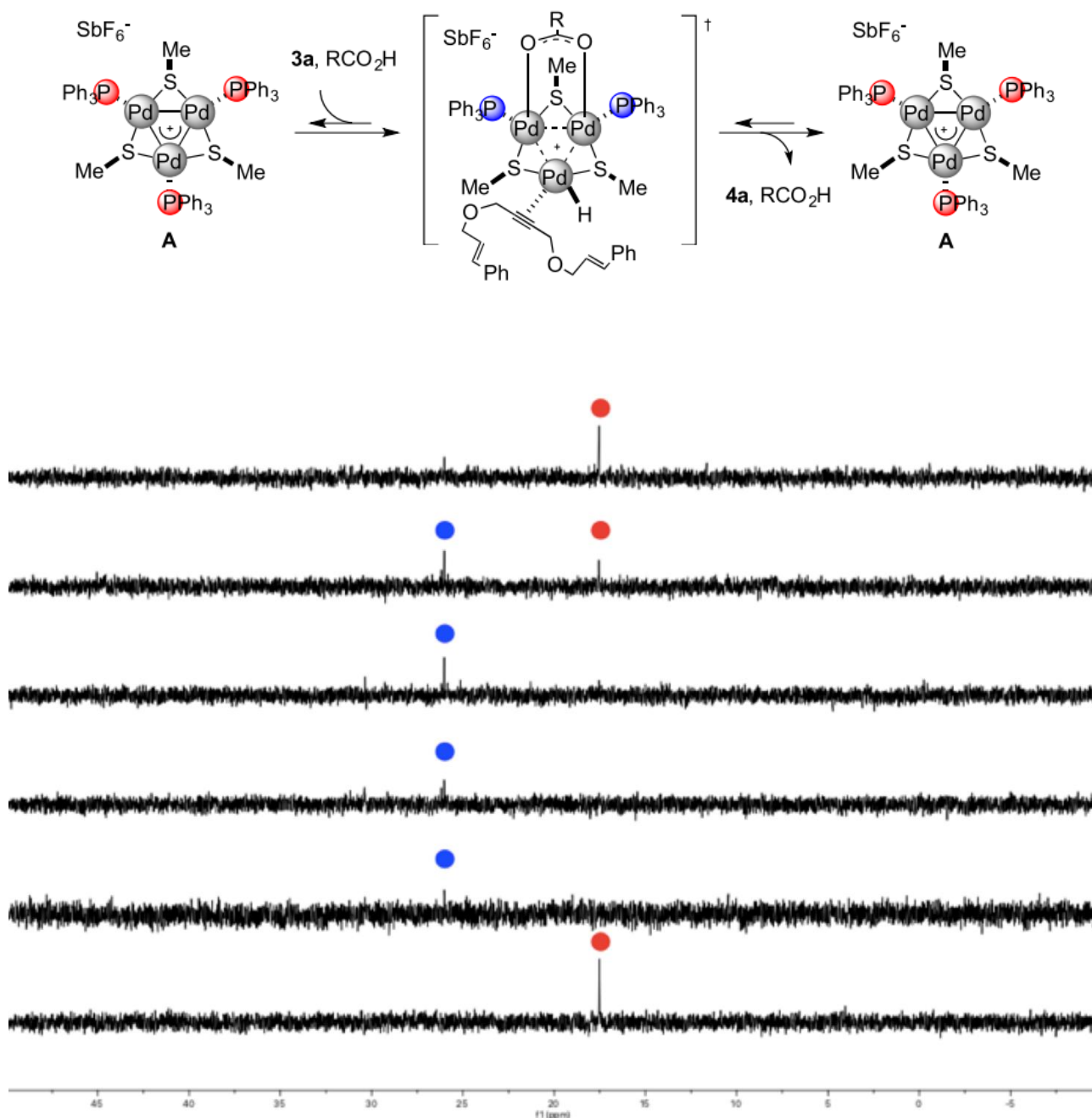


Figure 8. ^{31}P NMR analyses on the cyclization of **3a**.

According to experiments, we can rationalize the reaction mechanism (Figure 9). The ligand exchange between a substrate molecule and a phosphine one of complex **A** affords intermediate **I**. This complex reacts with a carboxylic acid (Figure 9 presents acetic acid because computational studies have been carried out using AcOH), providing the metal hydride **II**. The alkyne can now insert into the Pd-H bond, producing **III**. At this point, the resulting species undergoes insertion of the alkene moiety (**IV**) and subsequent β -hydride elimination affords the intermediate **Ia** and regenerates the metal-hydride (**V**). Finally, an intramolecular inverse electron demand Diels Alder reaction occurs via diene-metal interaction. This mechanism was confirmed carrying out other DFT calculations too.⁷⁹

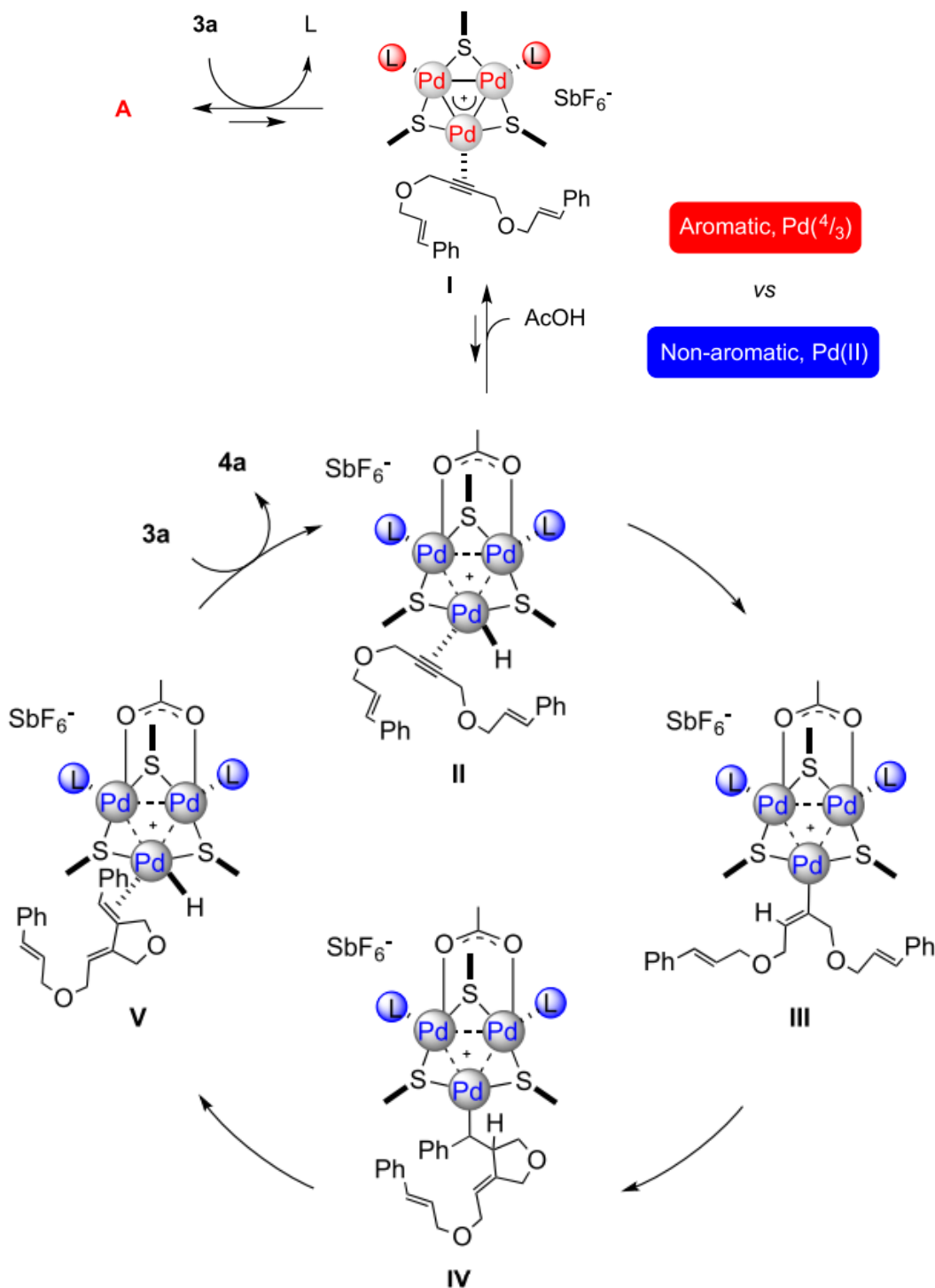


Figure 9. Plausible reaction mechanism

Conclusion

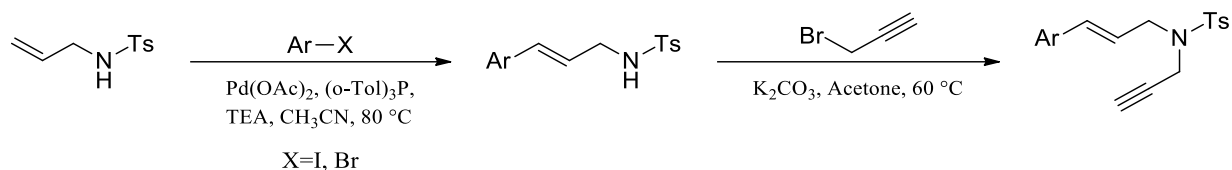
We described a reaction catalyzed by metalloaromatic compounds delivering polycycles through a C-C forming sequence. This synthetic procedure allowed the formation of complex molecule from simple substrates in an atom economical fashion. Study of the reaction mechanism provides more informations regarding analogies and differences between the present trinuclear cluster and other mononuclear palladium catalysts already reported in the literature. We hope that this work could be advantageous for developing stable and chemically robust homogeneous complexes in the future.

Experimental section

General Remarks.

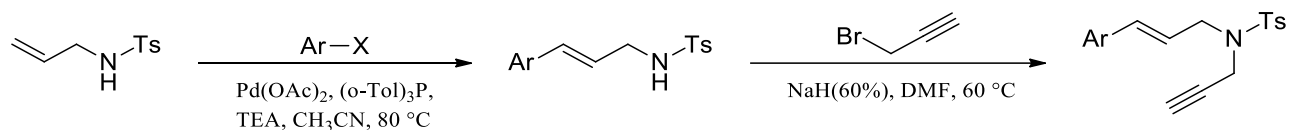
All chemicals were purchased from commercial sources and used as received. Solvents were dried and stored over molecular sieves previously activated in an oven (450 °C overnight). Prior to use, they were degassed by bubbling argon or N₂ for at least 30 min. Reactions, and the filtration for the synthesis of complex **A**, were carried out under nitrogen using the standard Schlenk technique. Catalytic reactions required the use of degassed solvents. Reactions that required warming were performed using high-vacuum-grade silicon oil as a liquid heat transfer agent. Chromatographic purifications were performed under gradient or isocratic regimes using a Combiflash system and prepacked disposable silica cartridges. ¹H NMR and ¹³C NMR spectra were recorded at 300 K on Bruker 400 MHz or Bruker 300 MHz spectrometers using the solvent as internal standard (7.26 ppm for ¹H NMR and 77.00 ppm for ¹³C NMR for CDCl₃). ¹⁹F NMR spectra were recorded at 376 MHz in CDCl₃ at 298 K on a Bruker 400 spectrometer fitted with a BBFO probehead. Reported assignments are based on decoupling, COSY, NOESY, HSQC, and HMBC correlation experiments. 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. Exact masses were recorded on an LTQ ORBITRAP XL Thermo Mass Spectrometer (electrospray source). MS analyses on reagents were collected on an Infusion Water Acquity Ultra Performance LC H06UPS-823M instrument with an SQ detector and ESI source. Enynes **1** and dienynes **3** were synthesized according to literature procedures.^{19,20} Spectroscopic data of **1a–d**, **1f–s**, **1u–v**, and **3a–e** correspond to those described in the literature.

General Procedure for the Synthesis of Enynes GP-1a.



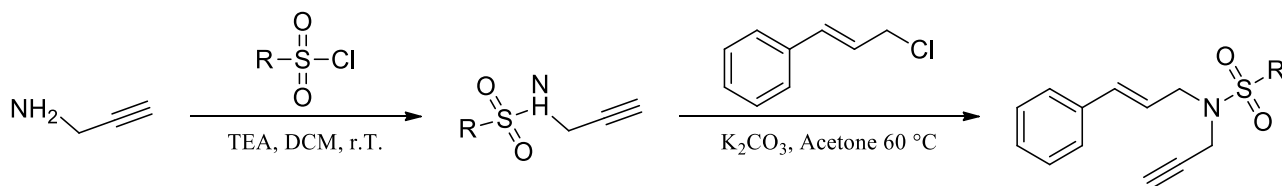
To a Schlenk tube equipped with a magnetic stirring bar, N-allyl-4-methylbenzenesulfonamide (2–10 mmol, 1 equiv), (o-Tol)₃P (0.1 equiv), and Pd(OAc)₂ (5 mol %) were added. CH₃CN (0.41 M), TEA (2 equiv), and the desired aryl halide (1 equiv) were added under a N₂ atmosphere, and the resulting mixture was stirred at 80 °C for 3 h. Then, an additional batch of the desired aryl halide (0.42 equiv), Pd(OAc)₂ (2.5 mol %), and (o-Tol)₃P (0.05 equiv) were added in this order. The mixture was stirred for an additional 6 h at 80 °C, cooled to r.T., diluted with water, and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel (n-hexanes/EtOAc 9:1). The resulting cinnamyl tosylamide (1.5–8 mmol, 1 equiv) was dissolved in acetone (0.2 M). Then, K₂CO₃ (3.0 equiv) and propargyl bromide (80% in toluene, 1.5 equiv) were sequentially added. The mixture was subsequently placed in a preheated oil bath at 60 °C and stirred overnight. After complete consumption of the starting material, monitored by TLC, the reaction mixture was cooled down to r.T. and water was added. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexanes/EtOAc 8:2).

General Procedure for the Synthesis of Enynes GP-1b.



N-Allyl-4-methylbenzenesulfonamide (2–10 mmol, 1 equiv), (o-Tol)₃P (0.1 equiv), and Pd(OAc)₂ (5 mol %) were sequentially added to a Schlenk tube equipped with a magnetic stirring bar. CH₃CN (0.41 M), TEA (2 equiv), and the desired aryl halide (1 equiv) were added under a N₂ atmosphere, and the mixture was stirred at 80 °C for 3 h. A second batch of the desired aryl halide (0.42 equiv), Pd(OAc)₂ (2.5 mol %), and (o-Tol)₃P (0.05 equiv) was then added. The mixture was stirred at 80 °C for a further 6 h, allowed to cool to room temperature, diluted with water, and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 9:1). The substituted cinnamyl tosylamide (1.5–8 mmol, 1 equiv) was dissolved in dry dimethylformamide (DMF) (0.2 M). Sodium hydride (60% dispersion in mineral oil, 1.1 equiv) and propargyl bromide (85% in toluene, 1.5 equiv) were then added at 0 °C. Once the evolution of dihydrogen ceased, the mixture was subsequently placed in a preheated oil bath at 60 °C and stirred overnight. After consumption of the starting material, the reaction mixture was cooled down to room temperature and water was added. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 8:2).

General Procedure for the Synthesis of Enynes GP-1c.



Dichloromethane (DCM) (0.4 M), TEA (1.1 equiv), and propargyl amine (2–10 mmol, 1 equiv) were added to a 100 mL round-bottom flask equipped with a magnetic stirring bar. The resulting mixture was stirred at 0 °C, and sulfonyl halide (1.05 equiv) was added slowly. The reaction mixture was stirred at room temperature for 12 h, quenched with sat NH_4Cl , diluted with DCM, and washed with water. The organic layer was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Without isolation, propargyl tosylamide was transferred in a Schlenk tube equipped with a magnetic stirring bar and K_2CO_3 (1.5 equiv) was added. Acetone (0.33 M) and cinnamyl chloride (1.3 equiv) were then added. The reaction mixture was stirred at 60 °C overnight. The mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 9:1).

General Procedure for the Synthesis of Enynes GP-1d.

The desired aryl halide was added (2–8 mmol, 1 equiv) to a mixture of $\text{Pd}(\text{OAc})_2$ (5 mol %), Ag_2CO_3 (0.6 equiv), and allyl acetate (2 equiv) in toluene (0.17 M). The resulting mixture was heated to reflux until complete conversion, which was monitored by TLC (usually within 6 h). After filtration on celite, the residue was dried under reduced pressure and then purified by flash chromatography affording the correspondent cinnamyl acetate (n-hexane/EtOAc 9:1), which was directly used for the next step. The desired cinnamyl acetate was added to a vigorously stirred suspension of K_2CO_3 (3 equiv) in MeOH (0.2 M), which was placed into a 100 mL round-bottom flask equipped with a magnetic stirring bar. The reaction mixture was stirred at r.T. overnight. After complete consumption of the starting material, MeOH was partially evaporated and the mixture was diluted with water and extracted twice with EtOAc (20 mL each). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexanes/EtOAc, under gradient) affording the correspondent cinnamyl alcohol. The resulting alcohol (1–5 mmol, 1 equiv) was dissolved in DMF (0.2 M), and NaH (60% in mineral oil, 1.3 equiv) was added slowly at 0 °C under vigorous stirring. The resulting mixture was stirred for 1 h at r.T. prior to the addition of propargyl bromide (80% in toluene, 1.5 equiv). The mixture was then stirred overnight. After completion, monitored by TLC, the mixture was quenched with water and extracted with EtOAc (2×20 mL). The concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexanes/EtOAc, under gradient).

General Procedure for the Synthesis of Symmetric Dienynes GP-2a.

Step 1: to a mixture of $\text{Pd}(\text{OAc})_2$ (51 mg, 0.23 mmol, 2.5 mol %) and Ag_2CO_3 (750 mg, 2.7 mmol, 0.33 equiv) in toluene (90 mL) were sequentially added the desired aryl halide (9.05 mmol, 1 equiv) and allyl acetate (1.95 mL, 18.1 mmol, 2 equiv). The resulting mixture was heated to reflux until complete conversion of the halide, which was monitored by TLC (usually within 6 h). Upon celite filtration, the residue was dried under reduced pressure and then purified by flash chromatography (n-hexane/EtOAc 9:1). Step 2: to a solution of but-2-yne-1,4-diol (1 equiv) in dry THF (0.5 M) was added dropwise Et_2Zn (1.05 equiv, 1 M in hexane). The resulting mixture was stirred until it turned cloudily white (30 min). Then, the previously prepared allyl acetate (2–7 mmol, 1.1 equiv) and $\text{Pd}(\text{PPh}_3)_4$ (10 mol %) were added. The reaction was stirred until complete conversion (monitored by TLC, 16 h). The mixture was then concentrated and carefully purified by flash chromatography to yield the symmetric diyne.

Synthesis of Nonsymmetric Dienynes (3f, 3g).

A solution of cinnamyl alcohol (94 mg, 0.7 mmol, 1 equiv) in THF (2 mL) was added to a suspension of NaH (60% in mineral oil, 36 mg, 0.9 mmol, 1.3 equiv) in DMF (2 mL) cooled at 0 °C. The resulting mixture was stirred for 30 min at 0 °C prior to the addition of the desired enynol (1 mmol, 1 equiv), which were prepared following the procedure described above using 2 equiv of but-2-yne-1,4-diol for Step 2. The resulting mixture was stirred at r.T. overnight. After completion, the mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with sat. LiCl, dried over Na₂SO₄, and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexanes/ EtOAc, gradient).

Synthesis of Tripalladium Catalysts.

Pd(dba)₂ (0.2 mmol, 115 mg, 1 equiv) was added to a 50 mL Schlenk tube. The vessel underwent three vacuum/N₂ cycles. Twenty milliliters of freshly degassed CHCl₃ were then syringed under N₂. The desired phosphine (0.2 mmol, 1 equiv) and the disulfide (0.1 mmol, 0.5 equiv) were added to the mixture. The resulting solution was kept under stirring at r.T. for 2 h, and AgSbF₆ (0.067 mmol, 23 mg, 0.33 equiv) was then added under N₂. Stirring was maintained for 1 h, and the mixture was then filtered through a short pad of celite under N₂ to remove traces of black metals. The solvent was removed under vacuum to leave a deep red solid that was purified by CHCl₃/hexane washings (1/30 v/ v, 3 × 30 mL). This purification afforded clusters as orange/red solids. For catalytic reactions, tripalladium complexes of higher purity were obtained after crystallization by vapor diffusion (n-Hex/CHCl₃). Spectroscopic data of complexes **A–D** correspond to the literature.^{75–77}

⁷⁵ Xu, H.-L.; Popov, I. A.; Tkachenko, N. V.; Wang, Z.-C.; MunozCastro, A.; Boldyrev, A. I.; Sun, Z.-M. *σ-Aromaticity-Induced Stabilization of Heterometallic Supertetrahedral Clusters [Zn₆Ge₁₆]⁴⁻ and [Cd₆Ge₁₆]⁴⁻*. *Angew. Chem., Int. Ed.* **2020**, 59, 17286. ⁷⁶ Wang, Z.-C.; Tkachenko, N. V.; Qiao, L.; Matito, E.; MunozCastro, A.; Boldyrev, A. I.; Sun, Z.-M. *All-metal σ-antiaromaticity in dimeric cluster anion {[CuGe₉Mes]₂}⁴⁻*. *Chem. Commun.* **2020**, 56, 6583. ⁷⁷ Liu, C.; Popov, I. A.; Chen, Z.; Boldyrev, A. I.; Sun, Z.-M. *Aromaticity and Antiaromaticity in Zintl Clusters*. *Chem. - Eur. J.* **2018**, 24, 14583.

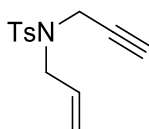
Catalytic Synthesis of **2** (GP-1).

Complex A (5.0 mg, 0.0031 mmol, 1 mol %) and freshly degassed toluene (5 mL) are added under nitrogen to a Schlenk-type flask equipped with a magnetic stirring bar and a septum. The desired substrate **1a–u** (0.3 mmol, 0.06 M) and benzoic acid (36.6 mg, 0.3 mmol, 1 equiv) were sequentially added. The mixture was heated at 100 °C, and the conversion was followed by TLC. Upon complete conversion of the substrate, the solution was diluted with 5 mL of DCM and washed with sat. NaHCO₃ (3 × 5 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (nhexanes/EtOAc, gradient).

Catalytic Synthesis of **4** (GP-2).

Complex A (2.5 mg, 1.68 μmol, 1 mol %) was added to a 2 mL vial flushed with nitrogen and equipped with a magnetic stirring bar and a septum. A solution of the desired substrate **3a–g** (0.168 mmol, 1 equiv) and benzoic acid (20.6 mg, 0.168 mmol, 1 equiv) in freshly degassed dry CHCl₃ (280 μL, 0.05 M) was then syringed. The mixture was heated at 45 °C (**3a**, **3b**, **3c**, **3e**) or 70 °C (**3d**, **3f**, **3g**), and the conversion was followed by TLC. Upon complete conversion of the substrate, the solution was diluted with 10 mL of DCM and washed with sat. NaHCO₃ (3 × 5 organic layers were washed with a sat. LiCl solution. The organic fraction was dried over Na₂SO₄ and mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexanes/EtOAc, gradient).

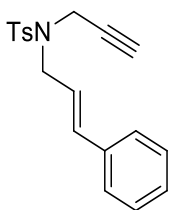
N-Allyl-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (**1a**).



Following the literature procedure, **1a** was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (1.9 g, 7.6 mmol, 77%). The spectral data for this compound correspond to the literature.⁶³ ¹H NMR (300 MHz, CDCl₃) δ = 7.74 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 5.73 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H), 5.32–5.22 (m, 2H), 4.09 (d, *J* = 2.4 Hz, 2H), 3.83 (d, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.00 (t, *J* = 2.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 143.6, 136.0, 131.9, 129.5, 127.8, 120.0, 76.5, 73.7, 49.0, 35.8, 21.6.

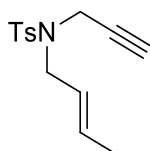
⁶³ Lanzi, M.; Cañeque, T.; Marchio, L.; Maggi, R.; Bigi, F.; Malacria, M.; Maestri, G. Alternative Routes to Tricyclic Cyclohexenes with Trinuclear Palladium Complexes. *ACS Catal.* **2018**, 8, 144

N -Cinnamyl-4-methyl- N -(prop-2-yn-1-yl)- benzenesulfonamide (1b).



Following the literature procedure, **1b** was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (1.9 g, 5.8 mmol, 90%). The spectral data for this compound correspond to the literature.⁶³ **¹H NMR** (300 MHz, CDCl₃) δ = 7.76 (d, J = 8.4 Hz, 2H), 7.35–7.24 (m, 8H), 6.57 (d, J = 15.7 Hz, 1H), 6.08 (dt, J = 15.7, 6.7 Hz, 1H), 4.13 (d, J = 2.4 Hz, 2H), 3.99 (d, J = 7.0 Hz, 2H), 2.43 (s, 3H), 2.05 (t, J = 2.4 Hz, 1H). **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ = 143.6, 136.11, 136.07, 135.0, 129.5, 128.6, 128.1, 127.8, 126.6, 122.9, 76.8, 73.8, 48.6, 35.9, 21.6.

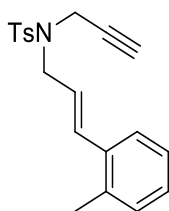
(E) -N-(But-2-en-1-yl)-4-methyl-N-(prop-2-yn-1-yl)- benzenesulfonamide (1c).



Following the literature procedure, **1c** was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (711 mg, 2.7 mmol, 90%). The spectral data for this compound correspond to the literature.⁶⁴ **¹H NMR** (400 MHz, CDCl₃) δ = 7.72 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.75–5.66 (m, 1H), 5.39–5.32 (m, 1H), 4.08–4.07 (m, 2H), 3.75 (d, J = 6.8 Hz, 2H), 2.42 (s, 3H), 1.99 (t, J = 2.6 Hz, 1H), 1.69–1.65 (m, 3H).

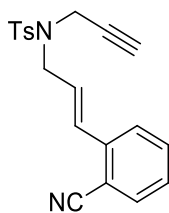
⁶⁴ Cecchini, C.; Lanzi, M.; Cera, G.; Malacria, M.; Maestri, G. Complementary Reactivity of 1,6-Enynes with All-Metal Aromatic Trinuclear Complexes and Carboxylic Acids. *Synthesis* **2019**, 51, 1216

(E)-4-Methyl-N-(prop-2-yn-1-yl)-N-(3-(o-tolyl)allyl)- benzenesulfonamide (1d).



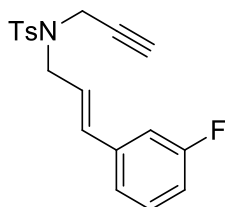
Following **GP-1a**, product 1d was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (500 mg, 1.47 mmol, 61%) The spectral data for this compound correspond to the literature.⁶⁴ **¹H NMR** (400 MHz, CDCl₃) δ = 7.77 (d, J = 8.4 Hz, 2H), 7.37–7.35 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.18–7.12 (m, 3H), 6.81 (d, J = 15.6 Hz, 1H), 5.95 (dt, J = 15.4, 6.9 Hz, 1H), 4.14 (d, J = 2.5 Hz, 2H), 4.01 (d, J = 6.9 Hz, 2H), 2.44 (s, 3H), 2.31 (s, 3H), 2.05 (s, 1H).

(E)-N-(3-(2-Cyanophenyl)allyl)-4-methyl-N-(prop-2-yn-1-yl)- benzenesulfonamide (1e).



Compound **1e** (229 mg, 0.65 mmol, 44% yield) was prepared adapting a literature procedure⁶⁴ and obtained as an orange solid (silica gel, n-hexane/EtOAc 8:2). ¹H NMR (400 MHz, CDCl₃) δ = 7.77 (d, J = 8.3 Hz, 2H), 7.65–7.51 (m, 3H), 7.38–7.30 (m, 3H), 7.02–6.85 (m, 1H), 6.33 (dt, J = 15.8, 6.9 Hz, 1H), 4.14 (d, J = 2.5 Hz, 2H), 4.05 (dd, J = 6.8, 1.4 Hz, 2H), 2.44 (d, J = 0.7 Hz, 3H), 2.09 (t, J = 2.5 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 143.9 (Cq), 139.3 (Cq), 135.6 (Cq), 133.0 (CH), 132.9 (CH), 130.4 (CH), 129.7 (CH), 128.9 (CH), 128.2 (CH), 127.8 (CH), 125.9 (CH), 117.6 (Cq), 111.2 (Cq), 76.2 (Cq), 74.4 (CH), 48.7 (CH₂), 36.5 (CH₂), 21.6 (CH₃). (ESI)-HRMS calcd for C₂₀H₁₈N₂NaO₂S [M + Na]⁺ 373.0981, found 373.0988.

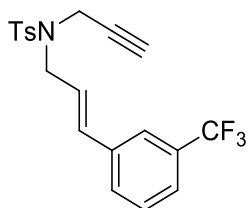
(E)-N-(3-(3-Fluorophenyl)allyl)-4-methyl-N-(prop-2-yn-1-yl)- benzenesulfonamide (1f).



Following **GP-1a**, product **1f** was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (328 mg, 0.95 mmol, 73%). The spectral data for this compound correspond to the literature.⁶⁵ ¹H NMR (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.27 (m, 1H), 7.09 (d, J = 7.7 Hz, 2H), 7.01 (m, 1H), 6.95 (tdd, J = 8.4, 2.5, 0.8, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.08 (dt, J = 15.8, 6.8 Hz, 1H), 4.13 (d, J = 2.5, 2H), 3.99 (dd, J = 6.8, 1.1, 2H), 6.44 (s, 3H), 2.06 (t, J = 2.5 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 143.8, 138.6, 138.5, 136.3, 136.1, 133.7, 130.2 (d, J = 8.5 Hz), 128.8 (d, J = 179.2 Hz), 124.6, 122.5, 115.0 (d, J = 21.4 Hz), 113.1 (d, J = 21.9 Hz), 74.0, 48.5, 36.2, 21.6. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ = 113.28.

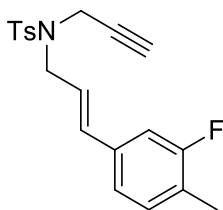
⁶⁵ Serafino, A.; Balestri, D.; Marchio, L.; Malacria, M.; Derat, E.; Maestri, G. *Orthogonal Syntheses of 3.2.0 Bicycles from Enallenes Promoted by Visible Light*. *Org. Lett.* **2020**, 22, 6354.

(E)-4-Methyl-N-(prop-2-yn-1-yl)-N-(3-(3-(trifluoromethyl)phenyl)allyl)benzenesulfonamide (1g).



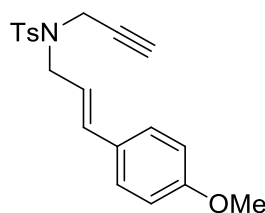
Following **GP-1b**, product **1g** was isolated (silica gel, n-hexane/EtOAc 8:2) as a colorless oil (216 mg, 0.55 mmol, 25%). The spectral data for this compound correspond to the literature.⁶⁴ **¹H NMR** (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.3 Hz, 2H), 7.54–7.50 (m, 3H), 7.45–7.41 (m, 1H), 7.31 (d, J = 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). **¹³C NMR** (101 MHz, CDCl₃) δ = 143.8, 136.9, 136.0, 133.2, 131.2 (q, J = 21.5 Hz), 129.6, 129.1, 127.7, 125.2, 123.8 (q, J = 272.2 Hz), 124.5 (q, J = 5.5 Hz), 123.2 (q, J = 4.8 Hz), 76.5, 74.0, 48.4, 36.2, 21.5. **¹⁹F NMR** (376 MHz, CDCl₃) δ = -62.5.

(E)-N-(3-(3-Fluoro-4-methylphenyl)allyl)-4-methyl-N-(prop2-yn-1-yl)benzenesulfonamide (1h).



Following **GP-1b**, product **1h** was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (294 mg, 0.82 mmol, 76%). The spectral data for this compound correspond to the literature.⁶⁴ **¹H NMR** (400 MHz, CDCl₃) 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). **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ = 161.4 (d, J = 242.4 Hz), 143.7, 136.2, 136.1 (d, J = 6.8 Hz), 133.7, 131.5, 129.6, 127.8, 123.9 (d, J = 9.8 Hz), 123.2, 122.1, 112.6 (d, J = 3.6 Hz), 76.6, 73.9, 48.5, 36.0, 21.6, 14.4. **¹⁹F{¹H} NMR** (376 MHz, CDCl₃) δ = 117.6.

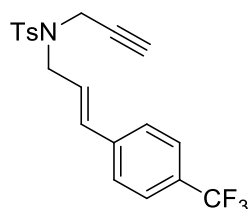
(E)-N-(3-(4-Methoxyphenyl)allyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (1i).



Following **GP-1a**, product **1i** was isolated (silica gel, n-hexane/EtOAc 8:2) as a colorless oil (186 mg, 0.52 mmol, 54%). The spectral data for this compound correspond to the literature.⁶⁶ **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ = 159.5, 143.5, 136.1, 134.5, 129.5, 128.9, 127.8, 127.7, 120.5, 114.0, 77.2, 73.7, 55.3, 48.6, 35.7, 21.5.

⁶⁶ Lanzi, M.; Santacroce, V.; Balestri, D.; Marchio, L.; Bigi, F.; Maggi, R.; Malacria, M.; Maestri, G. *Visible-Light Promoted Polycyclizations of Dienynes*. *Angew. Chem., Int. Ed.* **2019**, 58, 6703.

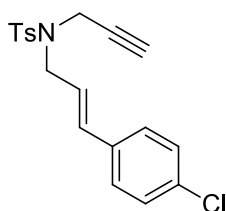
(E)-4-Methyl-N-(prop-2-yn-1-yl)-N-(3-(4-(trifluoromethyl)phenyl)allyl)benzenesulfonamide (1j).



Following **GP-1a**, product **1j** was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (195 mg, 0.49 mmol, 29%). The spectral data for this compound correspond to the literature.⁶⁷ **¹H NMR** (300 MHz, CDCl₃) δ = 7.79 (d, J = 8.3 Hz, 2H), 7.37–7.30 (m, 4H), 6.62 (d, J = 16.1 Hz, 2H), 6.18 (dt, J = 15.9, 6.7 Hz, 1H), 4.16 (d, J = 2.5 Hz, 2H), 4.04 (dd, J = 6.7, 1.4 Hz, 2H), 2.46 (s, 3H), 2.09 (t, J = 2.5 Hz, 1H).

⁶⁷ Ren, S. C.; Zhang, F. L.; Qi, J.; Huang, Y. S.; Xu, A. Q.; Yan, H. Y.; Wang, Y. F. *Radical Borylation/Cyclization Cascade of 1,6-Enynes for the Synthesis of Boron-Handled Hetero- and Carbocycles*. *J. Am. Chem. Soc.* **2017**, 139, 6050.

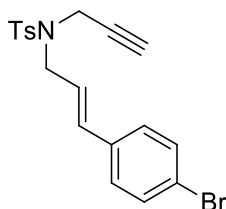
(E)-N-(3-(4-Chlorophenyl)allyl)-4-methyl-N-(prop-2-yn-1-yl) benzenesulfonamide (1k).



Following **GP-1a**, product **1k** was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (254 mg, 0.7 mmol, 80%). The spectral data for this compound correspond to the literature.⁶⁸ ¹H NMR (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.2 Hz, 2H), 7.31–7.23 (m, 6H), 6.51 (d, J = 15.8 Hz, 1H), 6.05 (dt, J = 15.8, 6.8 Hz, 1H), 4.11 (d, J = 2.4 Hz, 2H), 3.98–3.96 (m, 2H), 2.42 (s, 3H), 2.04 (s, 1H).

⁶⁸ Zhang, T.; Fu, L.; Gutekunst, W. R. *Practical Synthesis of Functional Metathesis Initiators Using Enynes. Macromolecules* **2018**, 51, 6497.

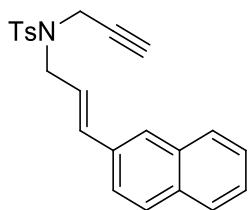
(E)-N-(3-(4-Bromophenyl)allyl)-4-methyl-N-(prop-2-yn-1-yl)- benzenesulfonamide (1l).



Following **GP-1a**, product **1l** was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (542 mg, 1.34 mmol, 64%). The spectral data for this compound correspond to the literature.⁶⁹ ¹H NMR (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.51 (d, J = 15.9 Hz, 1H), 6.08 (dt, J = 15.8, 6.8 Hz, 1H), 4.12 (d, J = 2.5 Hz, 2H), 3.98 (dd, J = 6.8, 1.3 Hz, 2H), 2.43 (s, 3H), 2.05 (t, J = 2.5 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 143.7 (Cq), 136.0 (Cq), 135.0 (Cq), 133.5 (CH), 131.8 (CH), 129.56(CH), 128.1 (CH), 127.8 (CH), 123.9 (CH), 121.9 (CH), 76.5 (Cq), 73.9 (CH), 48.5 (CH₂), 36.0 (CH₂), 21.6 (CH₃). (ESI)- MS calcd for C₁₉H₁₈BrNNaO₂S [M + Na]⁺ 428.01, found 427.76.

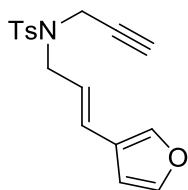
⁶⁹Dieckmann, M.; Jang, Y. S.; Cramer, N. *Chiral Cyclopentadienyl Iridium(III) Complexes Promote Enantioselective Cycloisomerizations Giving Fused Cyclopropanes. Angew. Chem., Int. Ed.* **2015**, 54, 12149

(E)-4-Methyl-N-(3-(naphthalen-2-yl)allyl)-N-(prop-2-yn-1-yl)benzenesulfonamide (1m).



Following **GP-1a**, product **1m** was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (476 mg, 1.27 mmol, 50%). The spectral data for this compound correspond to the literature.⁶⁴ **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C NMR** (75 MHz, CDCl₃) 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.

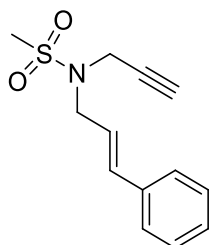
(E)-N-(3-(Furan-3-yl)allyl)-4-methyl-N-(prop-2-yn-1-yl)- benzenesulfonamide (1n).



Following **GP-1a**, product **1n** was isolated (silica gel, n-hexane/EtOAc 8:2) as a colorless oil (255 mg, 0.81 mmol, 67%). The spectral data for this compound correspond to the literature.⁶⁹ **¹H NMR** (300 MHz, CDCl₃) δ = 7.77 (d, J = 8.3 Hz, 2H), 7.42–7.28 (m, 4H), 6.50 (brs, 1H), 6.47 (d, J = 16.5 Hz, 1H), 5.82 (dt, J = 15.7, 6.9 Hz, 1H), 4.14 (d, J = 2.5 Hz, 2H), 3.96 (d, J = 1.3 Hz, 2H), 2.45 (s, 3H), 2.05 (t, J = 2.5 Hz, 1H).

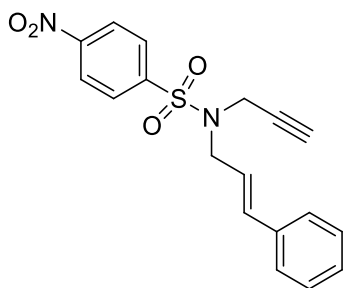
⁶⁹ Dieckmann, M.; Jang, Y. S.; Cramer, N. *Chiral Cyclopentadienyl Iridium(III) Complexes Promote Enantioselective Cycloisomerizations Giving Fused Cyclopropanes*. *Angew. Chem., Int. Ed.* **2015**, 54, 12149

N-Cinnamyl-N-(prop-2-yn-1-yl)methanesulfonamide (1o).



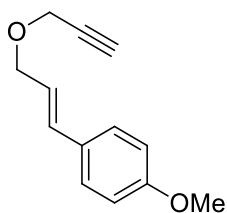
Following **GP-1c**, product **1o** was isolated (silica gel, n-hexane/ EtOAc 9:1) as a white solid (4.4 g, 17.6 mmol, 92%). The spectral data for this compound correspond to the literature.⁶⁴ **¹H NMR** (400 MHz, CDCl₃) δ = 7.41–7.26 (m, 5H), 6.67 (d, J = 15.8 Hz, 1H), 6.17 (dt, J = 15.8, 6.8 Hz, 2H), 4.11 (d, J = 2.5 Hz, 3H), 4.06 (dd, J = 6.8, 1.3 Hz, 3H), 2.99 (s, 4H). **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ = 135.9, 135.0, 128.6, 128.1, 126.5, 122.7, 77.3, 74.4, 48.7, 38.4, 35.7.

N-Cinnamyl-4-nitro-N-(prop-2-yn-1-yl)benzenesulfonamide (1p).



Following **GP-1c**, product **1p** was isolated (silica gel, n-hexane/ EtOAc 9:1) as a yellow oil (1.39 g, 3.9 mmol, 71%). The spectral data for this compound correspond to the literature.⁶⁵ **¹H NMR** (400 MHz, CDCl₃) δ = 8.36 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.8 Hz, 2H), 7.38–7.24 (m, 5H), 6.61 (d, J = 15.8 Hz, 1H), 6.10 (dt, J = 15.7, 6.9 Hz, 1H), 4.20 (d, J = 2.4 Hz, 2H), 4.04 (dd, J = 6.8, 1.2 Hz, 2H), 2.06 (t, J = 2.4 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 150.2 (Cq), 144.9 (Cq), 135.8 (CH), 135.7 (Cq), 129.1 (CH), 128.7 (CH), 128.4 (CH), 126.6 (CH), 124.2 (CH), 121.9 (CH), 75.9 (Cq), 74.5 (CH), 48.9 (CH₂), 36.0 (CH₂). **(ESI)-MS** calcd for C₁₈H₁₆N₂NaO₄S [M + Na]⁺ 379.34, found 378.97.

(E)-1-Methoxy-4-(3-(prop-2-yn-1-yloxy)prop-1-en-1-yl)- benzene (1q).

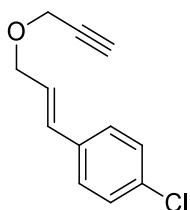


Following **GP-1d**, product **1q** was isolated (silica gel, n-hexane/EtOAc under gradient) as a yellow oil (136 mg, 0.67 mmol, 62%). The spectral data for this compound correspond to the literature.⁷⁰

¹H NMR (400 MHz, CDCl₃) δ = 7.36 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.61 (d, J = 15.9 Hz, 1H), 6.16 (dt, J = 15.9, 6.4 Hz, 1H), 4.28–4.18 (m, 4H), 3.83 (s, 3H), 2.48 (t, J = 2.4 Hz, 1H). **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ = 159.4 (Cq), 133.2 (CH), 129.3 (Cq), 127.8 (CH), 122.7 (CH), 114.0 (CH), 79.8 (Cq), 74.4 (CH), 70.4 (CH₂), 56.9 (CH₂), 55.3 (CH₃). **(ESI)-MS** calcd for C₁₃H₁₄NaO₂ [M + Na]⁺ 225.09, found 225.01.

⁷⁰ Pal, S.; Lucarini, F.; Ruggi, A.; Kilbinger, A. F. M. *Functional Metathesis Catalyst Through Ring Closing Enyne Metathesis: One Pot Protocol for Living Heterotelechelic Polymers*. *J. Am. Chem. Soc.* **2018**, 140, 3181

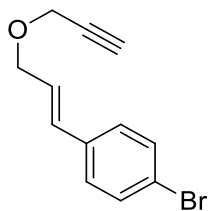
(E)-1-Chloro-4-(3-(prop-2-yn-1-yloxy)prop-1-en-1-yl)- benzene (1r).



Following **GP-1d**, product **1r** was isolated (silica gel, n-hexane/EtOAc under gradient) as a yellow oil (94 mg, 0.45 mmol, 61%). The spectral data for this compound correspond to the literature.⁷¹ **¹H NMR** (400 MHz, CDCl₃) δ = 7.35–7.26 (m, 4H), 6.60 (d, J = 15.9 Hz, 1H), 6.25 (dt, J = 16.0, 6.1 Hz, 1H), 4.23 (dd, J = 6.1, 1.5 Hz, 2H), 4.20 (d, J = 2.4 Hz, 2H), 2.46 (t, J = 2.4 Hz, 1H). **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ = 135.0 (Cq), 133.5 (Cq), 132.0 (CH), 128.8 (CH), 127.7 (CH), 125.8 (CH), 79.6 (Cq), 74.6 (CH), 70.0 (CH₂), 57.2 (CH₂). **(ESI)-MS** calcd for C₁₂H₁₂ClO [M + H]⁺ 207.06, found 207.11.

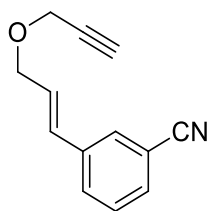
⁷¹ Hayashi, N.; Hirokawa, Y.; Shibata, I.; Yasuda, M.; Baba, A. *Hydroindation of Allenes and Its Application to Radical Cyclization*. *Org. Biomol. Chem.* **2008**, 6, 1949.

(E)-1-Bromo-4-(3-(prop-2-yn-1-yloxy)prop-1-en-1-yl)- benzene (1s).



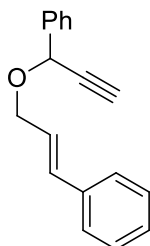
Following **GP-1c**, product **1s** was isolated (silica gel, n-hexane/EtOAc 9:1) as a yellow oil (153 mg, 0.61 mmol, 69%). The spectral data for this compound correspond to the literature.⁷⁰ **¹H NMR** (400 MHz, CDCl₃) δ = 7.46 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 16.0 Hz, 1H), 6.29 (dt, J = 15.9, 6.1 Hz, 1H), 4.30–4.18 (m, 4H), 2.49 (t, J = 2.4 Hz, 1H). **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ = 135.5 (Cq), 132.0 (CH), 131.7 (CH), 128.1 (CH), 125.9 (CH), 121.6 (Cq), 79.6 (Cq), 74.7 (CH), 70.0 (CH₂), 57.3 (CH₂). **(ESI)-MS** calcd for C₁₂H₁₁BrNaO [M + Na]⁺ 272.99, found 272.59.

(E)-3-(3-(Prop-2-yn-1-yloxy)prop-1-en-1-yl)benzonitrile (1t).



Compound **1t** (243 mg, 1.23 mmol, 56% yield) was prepared adapting a literature procedure⁶⁴ and obtained as a colorless oil (silica gel, n-hexane/EtOAc 8:2). **¹H NMR** (400 MHz, CDCl₃) δ = 7.67 (s, 1H), 7.62 (dt, J = 7.9, 1.6 Hz, 1H), 7.55 (dt, J = 7.6, 1.4 Hz, 1H), 7.49–7.40 (m, 1H), 6.66 (d, J = 15.9 Hz, 1H), 6.37 (dt, J = 16.0, 5.7 Hz, 1H), 4.29 (dd, J = 5.8, 1.5 Hz, 2H), 4.24 (d, J = 2.4 Hz, 2H), 2.50 (t, J = 2.4 Hz, 1H). **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ = 137.9 (Cq), 131.0 (CH), 130.6 (CH), 130.4 (CH), 130.0 (CH), 129.4 (CH), 128.2 (CH), 118.7 (Cq), 112.9 (Cq), 79.4 (Cq), 74.8 (CH), 69.6 (CH₂), 57.5 (CH₂). **(ESI)-HRMS** calcd for C₁₃H₁₁NNaO [M + Na]⁺ 220.0733, found 220.0725.

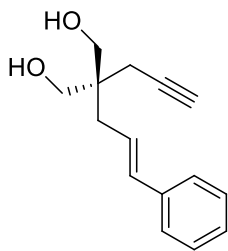
(E)-(3-(Prop-2-yn-1-yloxy)prop-1-ene-1,3-diyl)dibenzene (1u).



(E)-1,3-Diphenylprop-2-en-1-ol (841 mg, 4 mmol, 1 equiv) was dissolved in DMF (5.2 mL 0.77 M), and NaH (60% in mineral oil, 1.2 equiv) was added slowly at 0 °C under vigorous stirring. The resulting mixture was stirred 1 h at r.T. before the addition of propargyl bromide (80% in toluene) (517 μ L, 4.6 mmol, 1.2 equiv) and then stirring was maintained overnight. After completion, monitored by TLC, the mixture was quenched with water and extracted with EtOAc (2 $\times$ 15 mL). The organic layers were washed with a sat. LiCl solution. The organic fraction was dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexanes/EtOAc, under gradient) affording product **1u** as a yellow oil (532 mg, 53%). The spectral data for this compound correspond to the literature.⁷² ¹H NMR (400 MHz, CDCl₃) δ = 7.48–7.37 (m, 6H), 7.36–7.30 (m, 3H), 7.30–7.22 (m, 1H), 6.70 (dd, J = 15.9, 1.0 Hz, 1H), 6.32 (dd, J = 15.9, 7.2 Hz, 1H), 5.24 (d, J = 6.2 Hz, 1H), 4.26 (dd, J = 15.7, 2.4 Hz, 1H), 4.18 (dd, J = 15.8, 2.4 Hz, 1H), 2.49 (t, J = 2.4 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 140.2 (Cq), 136.4 (Cq), 132.4 (CH), 129.2 (CH), 128.6 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 127.1 (CH), 126.7 (CH), 80.9 (CH), 79.9 (Cq), 74.5 (CH₂), 55.3 (CH). (ESI)-MS calcd for C₁₈H₁₆NaO [M + Na]⁺ 271.31, found 271.11.

⁷² Scholz, S. O.; Kidd, J. B.; Capaldo, L.; Flikweert, N. E.; Littlefield, R. M.; Yoon, T. P. *Construction of Complex Cyclobutane Building Blocks by Photosensitized [2 + 2] Cycloaddition of Vinyl Boronate Esters*. *Org. Lett.* **2021**, 23, 3496.

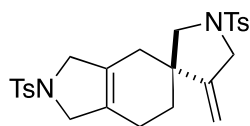
2-Cinnamyl-2-(prop-2-yn-1-yl)propane-1,3-diol (**1v**).



Product **1v** was prepared following a reported procedure⁷³ and was isolated (silica gel, n-hexane/EtOAc 8:2) as a white solid (212 mg, 0.9 mmol, 71%). The spectral data for this compound correspond to the literature.⁷⁴ ¹H NMR (400 MHz, CDCl₃) δ = 7.38–7.34 (m, 2H), 7.33–7.28 (m, 2H), 7.24–7.20 (m, 1H), 6.49 (d, J = 15.6 Hz, 1H), 6.22 (dt, J = 15.5, 7.7 Hz, 1H), 3.70 (s, 4H), 2.42 (s, 2H), 2.35–2.29 (m, 4H), 2.07 (t, J = 2.7 Hz, 1H).

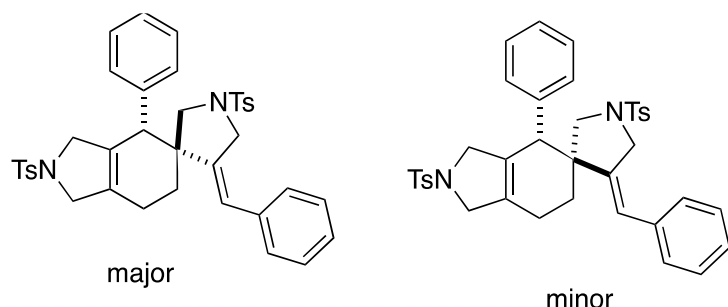
⁷³ Ramana, C. V.; Induvadana, B. A formal synthesis of (+)-didemniserinolipid B employing a Pd-mediated 6-endo selective alkynediol cycloisomerization. *Tetrahedron Lett.* **2009**, 50, 271. ⁷⁴ Miller, R.; Carreras, J.; Muratore, M. E.; Gaydou, M.; Camponovo, F.; Echavarren, A. M. *Broad Scope Aminocyclization of Enynes with Cationic JohnPhos–Gold(I) Complex as the Catalyst. J. Org. Chem.* **2016**, 81, 1839

4'-Methylene-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro- [isoindole-5,3'-pyrrolidine] (2a).



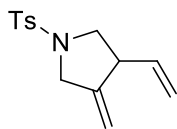
Compound **2a** (33.6 mg, 0.067 mmol, 45% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1a** (0.3 mmol); ¹H NMR (300 MHz, CDCl₃) δ = 7.69 (dd, *J* = 17.6, 8.3 Hz, 4H), 7.33 (dd, *J* = 7.7, 5.3 Hz, 4H), 4.87 (t, *J* = 1.9 Hz, 1H), 4.73 (t, *J* = 2.4 Hz, 1H), 3.97 (m, 2H), 3.85 (m, 4H), 2.99–2.92 (m, 2H), 2.44 (s, 6H), 1.91–1.84 (m, 4H), 1.67–1.47 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ = 151.2 (Cq), 143.8 (Cq), 143.5 (Cq), 134.4 (Cq), 132.6 (Cq), 129.8 (CH), 129.7 (CH), 129.6 (CH), 128.6 (CH), 127.7 (CH), 127.4 (CH), 106.0 (CH₂), 57.6 (CH₂), 56.7 (CH₂), 52.0 (2CH₂), 44.5 (Cq), 32.9 (CH₂), 30.3 (CH₂), 21.5 (2CH₃), 20.8 (CH₂). HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₂₆H₃₀N₂NaO₄S₂ 521.1540, found 521.1538.

(4S,5R)-4'-((Z)-Benzylidene)-4-phenyl-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] and **(4S,5S)-4'-((Z)-Benzylidene)-4-phenyl-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine]** (**2b/2b'**).



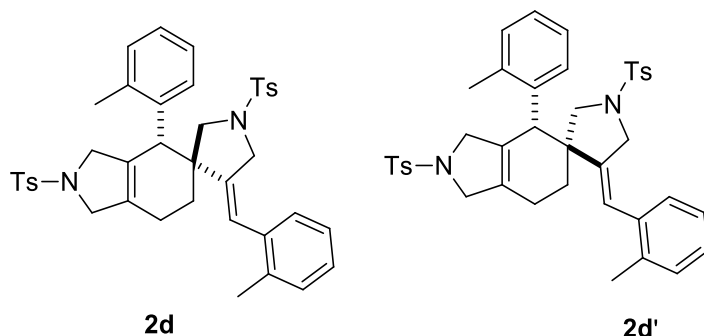
Compounds **2b** (major)/**2b'** (minor) (59.5 mg, 0.091 mmol, 61% yield, $^1\text{H NMR}$ ratio 43:57) were obtained as a white solid (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1b** (0.3 mmol); using 1.5 mmol of **1b** (488 mg) led to the recovery of **2b/2b'** mixture in a 74% yield (356 mg, 0.55 mmol, $^1\text{H NMR}$ ratio 38:62). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.72–7.63 (m, 5H), 7.54–7.51 (m, 1H), 7.35–7.09 (m, 14H), 7.01–6.90 (m, 2H), 6.75–6.71 (m, 4H), 6.04 (s, 1H), 5.06 (s, 1H), 4.37 (d, $J = 14.8$ Hz, 1H), 4.26 (d, $J = 14.6$ Hz, 1H), 4.18–4.09 (m, 4H), 3.88 (d, $J = 15.1$ Hz, 1H), 3.83–3.79 (m, 4H), 3.73 (d, $J = 14.9$ Hz, 1H), 3.55 (d, $J = 9.5$ Hz, 1H), 3.24 (s, 1H), 3.16 (s, 1H), 2.85 (d, $J = 9.6$ Hz, 1H), 2.79 (d, $J = 9.4$ Hz, 1H), 2.60 (d, $J = 9.8$ Hz, 1H), 2.46–2.35 (m, 16H), 2.23–2.10 (m, 1H), 2.03–1.99 (m, 2H), 1.82–1.74 (m, 2H), 1.35–1.23 (m, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 143.9 (Cq), 143.6 (Cq), 143.4 (Cq), 143.4 (Cq), 142.1 (Cq), 139.6 (Cq), 138.4 (Cq), 137.9 (Cq), 136.0 (CH), 134.2 (Cq), 133.8 (Cq), 132.8 (Cq), 132.6 (Cq), 132.4 (Cq), 130.9 (Cq), 130.8 (Cq), 130.7 (Cq), 129.8 (CH), 129.8 (CH), 129.7 (CH), 129.6 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.2 (CH), 127.8 (CH), 127.8 (CH), 127.5 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 124.7 (CH), 121.9 (CH), 57.5 (CH_2), 57.2 (CH_2), 57.0 (CH_2), 56.3 (CH_2), 56.0 (2 CH_2), 51.1 (CH_2), 50.7 (CH_2), 50.2 (Cq), 49.2 (Cq), 47.4 (CH), 47.1 (CH), 27.9 (CH_2), 26.0 (CH_2), 21.5 (CH_3), 21.5 (CH_3), 21.4 (CH_3), 21.4 (CH_3), 21.1 (CH_2), 20.5 (CH_2). (ESI)-HRMS $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{38}\text{H}_{38}\text{N}_2\text{NaO}_4\text{S}_2$ 673.2165, found 673.2163.

3-Methylene-1-tosyl-4-vinylpyrrolidine (**2c**).



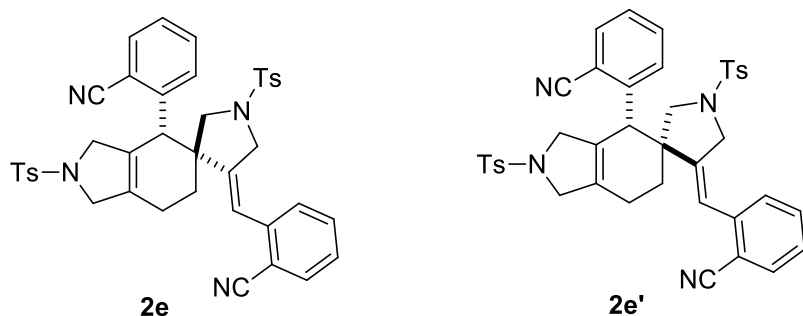
Compound **2c** (66.6 mg, 0.25 mmol, 84% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure GP-1 from **1c** (0.3 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.50 (ddd, *J* = 16.3, 10.9, 8.2 Hz, 1H), 5.13 (m, 1H), 5.10–5.08 (m, 1H), 4.97 (dd, *J* = 4.4, 2.2 Hz, 1H), 4.86 (d, *J* = 2.4 Hz, 1H), 3.99 (ddd, *J* = 14.2, 3.3, 2.2 Hz, 1H), 3.71 (dq, *J* = 14.1, 2.0 Hz, 1H), 3.62 (dd, *J* = 9.4, 7.9 Hz, 1H), 3.24 (q, *J* = 8.1 Hz, 1H), 2.85 (t, *J* = 9.2 Hz, 2H), 2.44 (s, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 146.8 (Cq), 143.8 (Cq), 135.7 (CH), 132.9 (Cq), 129.8 (2CH), 128.0 (2CH), 118.2 (CH₂), 108.4 (CH₂), 53.3 (CH₂), 52.0 (CH₂), 47.8 (CH), 21.7 (CH₃). (ESI)-HRMS calcd for C₁₄H₁₈NO₂S [M + H]⁺ 264.1058, found 264.1051.

(4S,5S)-4'-((Z)-2-Methylbenzylidene)-4-(o-tolyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] and **(4S,5R)-4'-((Z)-2-Methylbenzylidene)-4-(o-tolyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine]** (**2d**/ **2d'**).



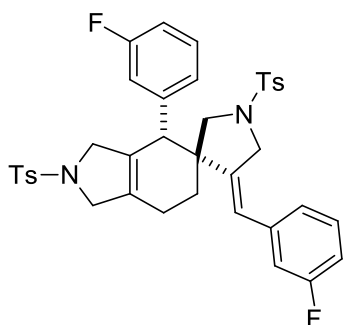
Compounds **2d** (**2d'**) (37.0 mg, 0.054 mmol, 54% yield, ^1H NMR ratio 57:43) were obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1d** (0.2 mmol); ^1H NMR (300 MHz, acetone- d_6) δ 7.83–7.78 (m, 2H), 7.72–7.64 (m, 6H), 7.46–7.31 (m, 9H), 7.23–7.18 (m, 2H), 7.11–7.01 (m, 10H), 6.95–6.89 (m, 2H), 6.65–6.60 (m, 1H), 6.11 (s, 1H), 5.24 (t, J = 2.1 Hz, 1H), 4.27 (dd, J = 14.8, 2.5 Hz, 1H), 4.22–4.18 (m, 4H), 4.13 (d, J = 2.7 Hz, 1H), 4.07 (dd, J = 6.5, 1.6 Hz, 2H), 3.98–3.93 (m, 2H), 3.80 (s, 2H), 4.75–3.61 (m, 5H), 3.57–3.54 (m, 2H), 3.39–3.34 (m, 1H), 2.89–2.85 (m, 6H), 2.73 (d, J = 9.6 Hz, 1H), 2.54–2.50 (m, 1H), 2.49–2.47 (m, 3H), 2.44 (s, 9H), 2.24–2.22 (m, 6H), 1.92–1.78 (m, 2H), 1.49–1.43 (m, 2H). ^{13}C NMR (75 MHz, acetone- d_6) δ = 144.8, 144.7, 144.4, 144.3, 143.7, 143.7, 141.6, 139.1, 138.5, 138.1, 137.4, 137.3, 136.7, 136.7, 136.6, 136.3, 135.5, 135.5, 134.6, 133.5, 133.4, 133.2, 132.4, 132.0, 131.9, 131.6, 131.2, 130.8, 130.7, 130.7, 130.7, 130.6, 130.6, 130.5, 130.4, 129.4, 128.9, 128.7, 128.7, 128.6, 128.5, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.7, 127.6, 127.3, 127.3, 126.8, 126.7, 126.6, 125.2, 123.9, 121.5, 59.7, 58.1, 58.0, 57.9, 57.3, 56.8, 52.6, 51.3, 51.1, 50.7, 49.6, 47.1, 44.0, 42.1, 21.6, 21.5, 21.4, 21.4, 21.3, 20.0, 20.0, 19.9, 19.5. (ESI)-HRMS calcd for $\text{C}_{40}\text{H}_{42}\text{N}_2\text{NaO}_4\text{S}_2$ $[\text{M} + \text{Na}]^+$ 701.2484, found 701.2477.

2-((3'R,4S,Z)-4'-(2-Cyanobenzylidene)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidin]-4-yl)- benzonitrile and 2-((3'S,4S,Z)-4'-(2-Cyanobenzylidene)-1',2- ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidin]-4-yl)benzonitrile (2e/2e').



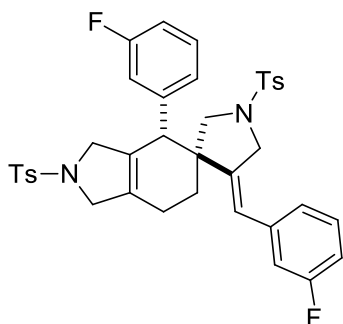
Compounds **2e/2e'** (35.3 mg, 0.050 mmol, 58% yield, $^1\text{H NMR}$ ratio 39:61) were obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1e** (0.178 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.74–7.43 (m, 16H), 7.40–7.24 (m, 13H), 7.23–7.15 (m, 2H), 7.01 (d, J = 7.8 Hz, 1H), 6.39 (s, 1H), 5.23 (s, 1H), 4.90 (dd, J = 15.2, 2.4 Hz, 1H), 4.30–4.08 (m, 4H), 3.99 (dd, J = 15.2, 2.2 Hz, 1H), 3.90–3.71 (m, 7H), 3.66 (dd, J = 15.2, 2.4 Hz, 1H), 3.49 (d, J = 9.8 Hz, 1H), 3.11 (d, J = 9.5 Hz, 1H), 3.01 (d, J = 9.8 Hz, 1H), 2.65 (d, J = 9.5 Hz, 1H), 2.48 (s, 3H), 2.43 (s, 6H), 2.32 (s, 3H), 2.30–2.17 (m, 3H), 2.16–1.97 (m, 3H), 1.78 (dt, J = 14.1, 7.2 Hz, 1H), 1.44 (dd, J = 13.2, 5.2 Hz, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 146.4 (Cq), 145.4 (Cq), 144.2 (Cq), 144.2 (Cq), 143.8 (Cq), 143.5 (Cq), 141.7 (Cq), 141.5 (Cq), 139.5 (Cq), 138.5 (Cq), 134.5 (Cq), 134.1 (Cq), 133.9 (Cq), 133.4 (CH), 133.2 (CH), 133.2 (CH), 133.0 (CH), 132.91 (Cq), 132.89 (CH), 132.8 (CH), 132.8 (CH), 132.7 (Cq), 132.6 (CH), 131.9 (Cq), 130.02 (CH), 129.95 (2CH), 129.9 (CH), 129.86 (Cq), 129.8 (2CH), 129.4 (Cq), 129.3 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.8 (CH), 127.6 (CH), 127.55 (2CH), 127.52 (2CH), 127.4 (CH), 121.8 (CH), 119.5 (CH), 117.80 (Cq), 117.77 (Cq), 117.5 (Cq), 117.1 (Cq), 115.0 (Cq), 113.5 (Cq), 112.5 (Cq), 111.9 (Cq), 57.4 (CH_2), 57.2 (CH_2), 56.9 (CH_2), 56.1 (CH_2), 56.0 (CH_2), 55.6 (CH_2), 52.1 (CH_2), 50.9 (Cq), 50.4 (Cq), 49.4 (CH_2), 45.4 (CH), 45.3 (CH), 28.3 (CH_2), 26.4 (CH_2), 21.7 (CH_3), 21.6 (2 CH_3), 21.5 (CH_3), 21.3 (CH_2), 20.4 (CH_2). (ESI)-HRMS calcd for $\text{C}_{40}\text{H}_{37}\text{N}_4\text{O}_4\text{S}_2$ 701.2251 $[\text{M} + \text{H}]^+$, found 701.2242.

(4S,5S)-4'-((Z)-3-Fluorobenzylidene)-4-(3-fluorophenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2f).



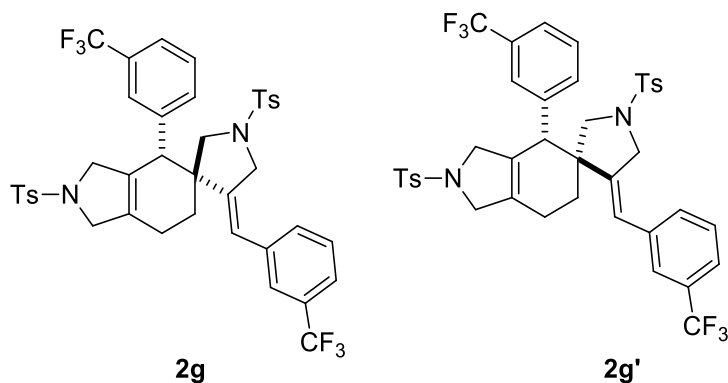
Compound **2f** (30.9 mg, 0.045 mmol, 43% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1f** (0.2 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.69 (m, 4H), 7.35 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.19 (td, J = 8.0, 6.3 Hz, 1H), 7.10 (td, J = 7.9, 6.2 Hz, 1H), 6.86 (ddd, J = 10.0, 8.4, 2.4 Hz, 2H), 6.57 (d, J = 7.4 Hz, 1H), 6.51 (d, J = 7.4 Hz, 1H), 6.43 (d, J = 10.1 Hz, 1H), 5.09 (s, 1H), 4.33 (dd, J = 15.0, 2.4 Hz, 1H), 4.17 (m, 2H), 3.83 (dd, J = 15.0, 2.4 Hz, 1H), 3.80 (m, 2H), 3.55 (d, J = 9.4 Hz, 1H), 3.19 (s, 1H), 2.77 (d, J = 9.4 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 1.95 (m, 2H), 1.36 (m, 2H), 1.26 (m, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 163.2 (d, $^1J_{\text{CF}}$ = 264 Hz), 162.8 (d, $^1J_{\text{CF}}$ = 264 Hz), 144.3 (Cq), 143.9 (Cq), 141.4 (d, $^3J_{\text{CF}}$ = 6.6 Hz, Cq), 138.1 (d, $^3J_{\text{CF}}$ = 7.7 Hz, Cq), 134.2 (Cq), 132.9 (Cq), 131.7 (Cq), 130.5 (Cq), 130.1 (2CH), 129.9 (d, $^3J_{\text{CF}}$ = 8.4 Hz, CH), 129.6 (d, $^3J_{\text{CF}}$ = 8.4 Hz, CH), 127.8 (2CH), 127.5 (2CH), 123.98 (CH), 123.97 (CH), 123.68 (Cq), 123.67 (CH), 114.7 (d, $^2J_{\text{CF}}$ = 21.8 Hz, CH), 114.5 (d, $^2J_{\text{CF}}$ = 14.4 Hz, CH), 114.2 (d, $^2J_{\text{CF}}$ = 14.4 Hz, CH), 57.6 (C1), 57.1 (CH_2), 56.4 (CH_2), 51.2 (CH_2), 50.5 (C4), 47.0 (Cq), 29.8 (CH_2), 26.1 (CH_2), 21.7 (CH_3), 21.3 (CH_3). $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ = -112.83. **(ESI)- HRMS** calcd for $\text{C}_{38}\text{H}_{36}\text{F}_2\text{N}_2\text{NaO}_4\text{S}_2$ $[\text{M} + \text{Na}]^+$ 709.1982, found 709.1976.

(4S,5R)-4'-((Z)-3-Fluorobenzylidene)-4-(3-fluorophenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2f').



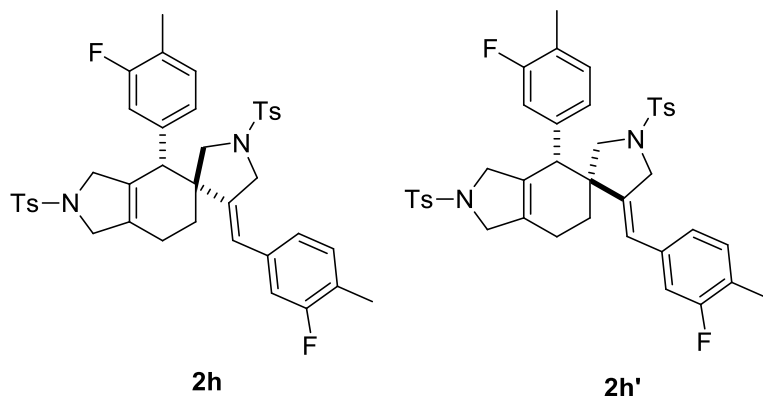
Compound **2f'** (20.6 mg, 0.030 mmol, 29% yield) was obtained (silica gel, n-hexanes/EtOAc, gradient) as a colorless oil (mixture with **2f**) following the general procedure **GP-1** from **1f** (0.2 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.65 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.38–7.26 (m, 4H), 7.23–7.18 (m, 1H), 6.97 (ddd, *J* = 10.8, 8.3, 2.3 Hz, 2H), 6.93–6.87 (m, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 6.9 Hz, 1H), 6.67 (d, *J* = 10.1 Hz, 1H), 6.57 (d, *J* = 8.5 Hz, 1H), 5.98 (s, 1H), 4.23 (dd, *J* = 15.0, 2.2 Hz, 1H), 4.17–4.07 (m, 2H), 3.93–3.82 (m, 2H), 3.71 (dd, *J* = 15.2, 2.0 Hz, 1H), 3.22 (s, 1H), 2.82 (d, *J* = 9.7 Hz, 1H), 2.63 (d, *J* = 9.6 Hz, 1H), 2.42 (s, 6H), 2.17–2.07 (m, 1H), 1.99–1.88 (m, 1H), 1.86–1.78 (m, 1H), 1.76–1.69 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 162.87 (d, ¹*J*_{CF} = 264.3 Hz, Cq), 162.84 (d, ¹*J*_{CF} = 264.8 Hz, Cq), 144.0 (d, ³*J*_{CF} = 6.6 Hz, Cq), 143.6 (Cq), 138.2 (d, 3 *J*_{CF} = 7.7 Hz, Cq), 133.8 (Cq), 133.3 (Cq), 132.6 (Cq), 130.2 (d, ³*J*_{CF} = 9.2 Hz, CH), 129.9 (d, ³*J*_{CF} = 9.1 Hz, CH), 127.7 (2CH), 127.5 (2CH), 124.1 (Cq), 121.3 (CH), 115.1 (d, ²*J*_{CF} = 21.8 Hz, CH), 114.9 (d, ²*J*_{CF} = 21.8 Hz, CH), 114.5 (d, ²*J*_{CF} = 21.3 Hz, CH), 57.4 (CH₂), 56.1 (CH₂), 50.8 (CH₂), 49.3 (Cq), 47.2 (CH), 27.9 (CH₂), 21.64 (CH₃), 21.59 (CH₃), 20.6 (CH₂). ¹⁹F NMR (376 MHz, CDCl₃) δ = −112.35. (ESI)-HRMS calcd for C₃₈H₃₆F₂N₂NaO₄S₂ [M + Na]⁺ 709.1982, found 709.1987.

(4*S*,5*S*)-1',2-Ditosyl-4'-((*Z*)-3-(trifluoromethyl)benzylidene)-4-(3-(trifluoromethyl)phenyl)-1,2,3,4,6,7-hexahydrospiro- [isoindole-5,3'-pyrrolidine] and (4*S*,5*R*)-1',2-Ditosyl-4'-((*Z*)-3-(trifluoromethyl)benzylidene)-4-(3-(trifluoromethyl)phenyl)-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (**2g**/**2g'**).



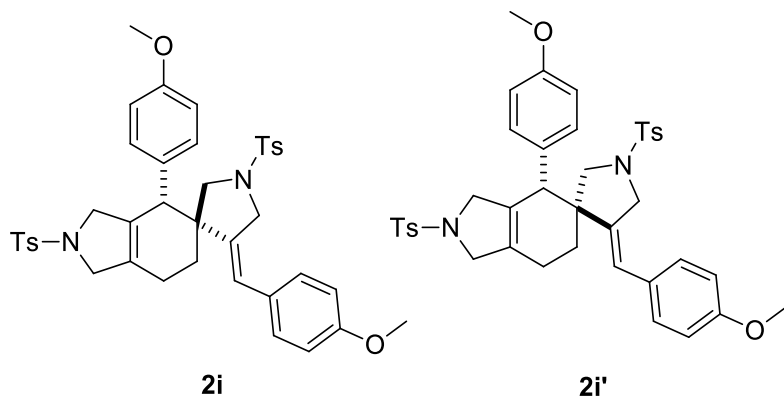
Compounds **2g/2g'** (51.4 mg, 0.065 mmol, 65% yield, $^1\text{H NMR}$ ratio 56:44) were obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1g** (0.2 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.73–7.65 (m, 7H), 7.59–7.48 (m, 6H), 7.44–7.21 (m, 15H), 7.02–6.99 (m, 2H), 6.91–6.89 (m, 2H), 6.15 (s, 1H), 5.08 (s, 1H), 4.36 (dd, J = 15.1, 2.7 Hz, 1H), 4.22–4.11 (m, 6H), 3.94–3.82 (m, 6H), 3.65–3.61 (m, 2H), 3.39 (s, 1H), 3.29 (s, 1H), 2.82 (d, J = 9.4 Hz, 2H), 2.59 (d, J = 9.6 Hz, 1H), 2.48 (s, 3H), 2.43 (s, 3H), 2.42 (s, 3H), 2.41 (s, 3H), 2.32–2.27 (m, 2H), 2.23–2.18 (m, 1H), 1.99–1.92 (m, 2H), 1.78–1.71 (m, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 144.2, 144.2, 144.0, 143.7, 141.7, 139.7, 138.9, 136.7, 136.2, 134.0, 133.8, 133.6, 132.5, 132.2, 131.2, 131.0, 130.9, 130.8, 130.5, 130.4 (2C), 130.3, 129.9, 129.9 (2C), 129.8 (2C), 129.8, 129.7, 129.2, 129.2, 128.9, 128.7, 128.5, 127.6, 127.5, 127.3 (3C), 127.1, 126.9, 125.2, 125.2, 125.1, 125.1, 125.0, 125.0, 124.7, 124.7, 124.6, 124.5, 124.2, 124.2, 124.1, 124.0, 123.9, 123.9, 123.9, 123.8, 121.2, 60.3, 57.5, 57.1, 56.9, 56.1, 55.8, 50.9, 50.7, 50.4, 49.2, 47.6, 47.0, 29.6, 25.8, 21.5, 21.4, 21.4, 21.1, 21.0, 20.5. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ = –62.6, –62.6, –62.7, –63.0. (ESI)-HRMS calcd for $\text{C}_{40}\text{H}_{37}\text{F}_6\text{N}_2\text{O}_4\text{S}_2$ [$\text{M} + \text{H}$] $^+$ 787.2099, found 787.2106.

(4S,5R)-4'-((Z)-3-Fluoro-4-methylbenzylidene)-4-(3-fluoro-4-methylphenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro- [isoindole-5,3'-pyrrolidine] and **(4S,5S)-4'-((Z)-3-Fluoro-4-methylbenzylidene)-4-(3-fluoro-4-methylphenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine]** (**2h/ 2h'**).



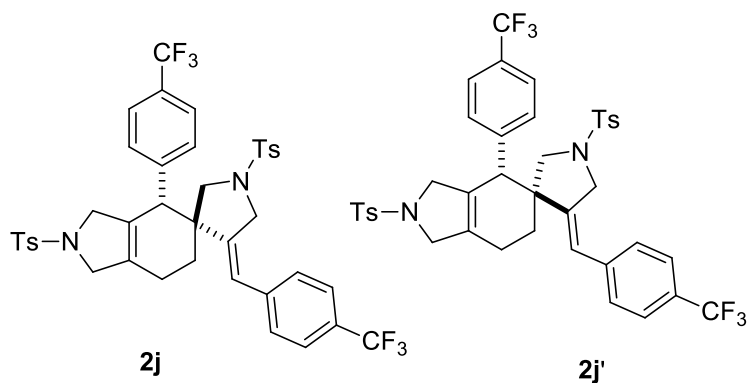
Compounds **2h/2h'** (57.0 mg, 0.080 mmol, 82% yield, $^1\text{H NMR}$ ratio 61:39) were obtained as a colorless oil (silica gel, nhexanes/EtOAc, gradient) following the general procedure GP-1 from **1h** (0.2 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.73–7.65 (m, 6H), 7.57 (d, J = 7.9 Hz, 2H), 7.37–7.29 (m, 7H), 7.15 (t, J = 8.0 Hz, 1H), 7.05 (t, J = 7.9 Hz, 2H), 6.93 (t, J = 8.0 Hz, 2H), 6.66 (dd, J = 25.1, 8.5 Hz, 4H), 6.46–6.37 (m, 4H), 5.95 (s, 1H), 5.09 (s, 1H), 4.34 (d, J = 16.3 Hz, 1H), 4.25 (d, J = 15.4 Hz, 1H), 4.18–4.07 (m, 6H), 3.87–3.80 (m, 4H), 3.72 (d, J = 15.2 Hz, 1H), 3.54 (d, J = 9.3 Hz, 1H), 3.19 (s, 1H), 3.14 (s, 1H), 2.83 (d, J = 9.6 Hz, 1H), 2.78 (d, J = 9.3 Hz, 1H), 2.65 (d, J = 9.8 Hz, 1H), 2.48 (s, 3H), 2.45–2.43 (m, 9H), 2.29 (s, 3H), 2.22 (s, 3H), 2.16 (s, 3H), 2.29–2.20 (m, 2H), 1.98 (m, 2H), 1.82–1.75 (m, 2H), 1.37–1.34 (m, 2H), 0.92–0.83 (m, 2H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 172.3 (d, J = 253.6 Hz), 161.1 (d, J = 244.7 Hz), 172.2 (d, J = 272.0 Hz), 160.9 (d, J = 244.6 Hz), 144.0 (2C), 143.7 (2C), 143.7 (2C), 143.6 (2C), 142.3, 140.1, 138.3, 138.2, 135.5, 135.4, 134.1, 133.7, 132.8, 132.8, 132.8, 132.5, 131.5, 131.4, 131.2 (2C), 131.2, 130.8, 130.8, 130.5, 130.3, 129.8, 129.8 (4C), 129.7, 127.6 (2C), 127.5, 127.3 (4C), 123.7, 123.5, 123.2, 122.0, 121.0, 114.6 (d, J = 22.8 Hz), 114.1 (d, J_{CF} = 22.7 Hz), 60.3, 59.8, 57.4, 57.2, 56.9, 56.3, 56.0, 56.0, 51.0, 50.6, 50.3, 49.1, 46.6, 46.5, 29.6, 27.7, 25.9, 21.5, 21.1, 21.0, 20.4, 14.2, 14.2, 14.1, 14.1. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ = –116.8, –117.3. (ESI)-HRMS calcd for $\text{C}_{40}\text{H}_{40}\text{F}_2\text{KN}_2\text{O}_4\text{S}_2$ $[\text{M} + \text{K}]^+$ 753.2035, found 753.2039.

(4S,5S)-4'-((Z)-4-Methoxybenzylidene)-4-(4-methoxyphenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] and (4S,5R)-4'-((Z)-4-Methoxybenzylidene)-4-(4-methoxyphenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2i/2i').



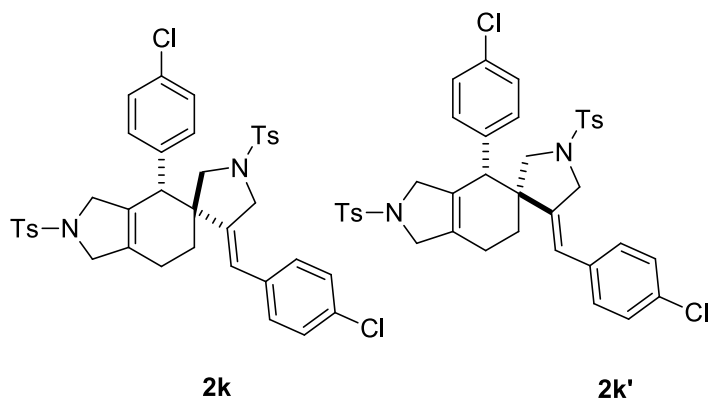
Compound **2i/2i'** (43.2 mg, 0.061 mmol, 62% yield, $^1\text{H NMR}$ ratio 65:35) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure GP-1 from **1l** (0.2 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.72 (d, J = 5.1 Hz, 8H), 7.66 (s, 2H), 7.56 (d, J = 7.7 Hz, 2H), 7.38–7.28 (m, 10H), 6.96–6.66 (m, 10H), 5.97 (s, 1H), 5.04 (s, 1H), 4.35 (d, J = 14.5 Hz, 2H), 4.19–4.11 (m, 4H), 3.91–3.71 (m, 10H), 3.71 (s, 6H), 3.54 (d, J = 9.2 Hz, 2H), 3.19 (s, 1H), 3.12 (s, 2H), 2.84 (d, J = 9.7 Hz, 1H), 2.79 (d, J = 9.3 Hz, 2H), 2.63 (d, J = 9.7 Hz, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 2.43 (s, 6H), 2.24–2.11 (m, 4H), 1.82–1.70 (m, 4H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 159.0, 158.8, 158.6, 158.5, 143.9, 143.6, 143.5, 143.4, 137.7, 134.4, 134.0, 132.2, 131.3, 131.1, 130.7, 130.6, 130.2, 129.9, 129.9, 129.8, 129.7, 129.6, 129.2, 128.9, 127.7, 127.6, 127.5, 127.4, 124.3, 121.3, 114.0, 113.9, 113.7, 113.3, 60.4, 57.5, 57.3, 57.0, 56.4, 56.1, 55.4, 55.3, 55.2, 51.3, 50.9, 50.4, 49.4, 49.4, 46.7, 46.4, 26.1, 21.6, 21.6, 21.3, 21.1, 20.6. **(ESI)-HRMS** calcd for $\text{C}_{40}\text{H}_{42}\text{KN}_2\text{O}_6\text{S}_2$ $[\text{M} + \text{K}]^+$ 749.2121, found 749.2127.

(4S,5S)-1',2-Ditosyl-4'-((Z)-4-(trifluoromethyl)benzylidene)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4,6,7-hexahydrospiro- [isoindole-5,3'-pyrrolidine] and (4S,5R)-1',2-Ditosyl-4'-((Z)-4-(trifluoromethyl)benzylidene)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2j/2j').



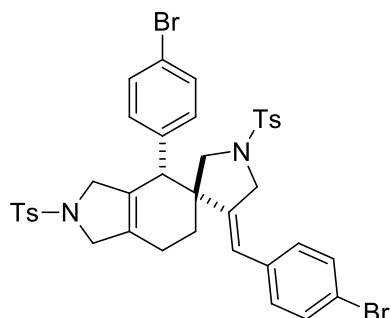
Compounds **2j/2j'** (56.0 mg, 0.071 mmol, 59% yield, $^1\text{H NMR}$ ratio 61:39) were obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1j** (0.2 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.71–7.68 (m, 5H), 7.65 (d, J = 8.2 Hz, 2H), 7.57–7.54 (m, 1H), 7.52–7.46 (m, 3H), 7.43–7.41 (m, 3H), 7.38–7.33 (m, 7H), 7.30–7.28 (m, 4H), 7.21–7.18 (m, 2H), 7.13–7.09 (m, 1H), 7.00–6.97 (m, 2H), 6.88–6.89 (m, 2H), 6.13 (s, 1H), 5.06 (s, 1H), 4.34 (dd, J = 15.1, 2.7 Hz, 1H), 4.24–4.11 (m, 5H), 3.92–3.79 (m, 5H), 3.63–3.59 (m, 2H), 3.36 (s, 1H), 3.27 (s, 1H), 2.80 (d, J = 9.5 Hz, 2H), 2.58 (d, J = 9.5 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 2.30–2.16 (m, 2H), 2.08–2.02 (m, 2H), 1.97–1.89 (m, 2H), 1.76–1.69 (m, 1H), 1.39 (dd, J = 13.2, 5.3 Hz, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 144.3, 144.2, 144.0, 143.8, 141.7, 139.7, 138.9, 136.7, 136.2, 134.0, 133.8, 133.7, 132.6, 132.1, 131.2, 131.0, 130.9, 130.6, 130.4, 130.0, 129.9, 129.8, 129.8, 129.2, 129.2, 128.9, 128.9, 128.7, 127.6, 127.6, 127.3, 125.1, 125.1, 125.0, 124.7, 124.7, 124.3, 124.2, 124.1, 124.1, 124.1, 124.0, 123.9, 123.8, 123.8, 122.5, 122.5, 122.4, 122.4, 121.2, 57.5, 57.1, 56.9, 56.2, 55.9, 55.8, 50.9, 50.7, 50.5, 49.2, 47.6, 47.0, 25.9, 21.5, 21.5, 21.5, 21.4, 20.6. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ = –62.6 (2F), –62.8, –63.0. **(ESI)-HRMS** calcd for $\text{C}_{40}\text{H}_{36}\text{F}_6\text{KN}_2\text{O}_4\text{S}_2$ $[\text{M} + \text{K}]^+$ 825.1658, found 825.1651.

(4S,5R)-4'-((Z)-4-Chlorobenzylidene)-4-(4-chlorophenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] and **(4S,5S)-4'-((Z)-4-Chlorobenzylidene)-4-(4-chlorophenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine]** (**2k/k'**).



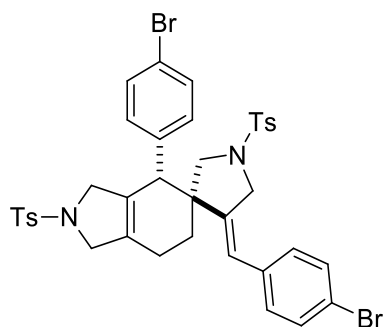
Compounds **2k/2k'** (63.0 mg, 0.088 mmol, 87% yield, $^1\text{H NMR}$ ratio 73:27) were obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1k** (0.2 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.72 (d, J = 2.9 Hz, 2H), 7.70 (d, J = 2.8 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.38–7.28 (m, 10H), 7.23 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 7.8 Hz, 2H), 6.70 (d, J = 9.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 6.05 (s, 1H), 5.04 (s, 1H), 4.34 (dd, J = 14.9, 2.6 Hz, 2H), 4.24–4.08 (m, 6H), 3.84–3.75 (m, 6H), 3.64 (dd, J = 14.8, 2.4 Hz, 1H), 3.57 (d, J = 9.3 Hz, 1H), 3.26 (s, 1H), 3.21 (s, 1H), 2.85 (d, J = 9.7 Hz, 1H), 2.77 (d, J = 9.3 Hz, 1H), 2.69–2.65 (m, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 2.44 (s, 6H), 1.97–1.69 (m, 3H), 1.45–1.34 (m, 2H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 144.1 (Cq), 143.8 (Cq), 143.6 (Cq), 143.6 (Cq), 142.9 (Cq), 140.3 (Cq), 137.0 (Cq), 136.3 (Cq), 134.3 (Cq), 134.2 (Cq), 134.2 (Cq), 133.9 (Cq), 133.6 (Cq), 133.2 (Cq), 133.1 (Cq), 133.0 (Cq), 133.0 (Cq), 132.7 (Cq), 132.5 (Cq), 131.5 (Cq), 130.5 (Cq), 130.3 (Cq), 129.9 (4CH), 129.8 (2CH), 129.7 (2CH), 129.5 (2CH), 129.0 (4CH), 128.8 (2CH), 128.6 (4CH), 128.6 (2CH), 128.1 (2CH), 127.6 (2CH), 127.5 (2CH), 127.4 (2CH), 127.4 (2CH), 123.9 (CH), 121.1 (CH), 57.4 (CH_2), 57.2 (CH_2), 56.9 (CH_2), 56.1 (CH_2), 55.8 (CH_2), 55.5 (CH_2), 51.1 (CH), 50.7 (Cq), 50.4 (2CH₂), 49.3 (CH), 47.2 (Cq), 46.5 (CH_2), 30.9 (CH_2), 25.9 (CH_3), 21.6 (CH_3), 21.5 (2CH₃), 21.1 (CH_2), 20.6 (CH_2). **(ESI)-HRMS** calcd for $\text{C}_{38}\text{H}_{36}\text{Cl}_2\text{KN}_2\text{O}_4\text{S}_2$ [$\text{M} + \text{K}$] $^+$ 757.1131, found 757.1125.

(3'S,4S,Z)-4'-(4-Bromobenzylidene)-4-(4-bromophenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2l).



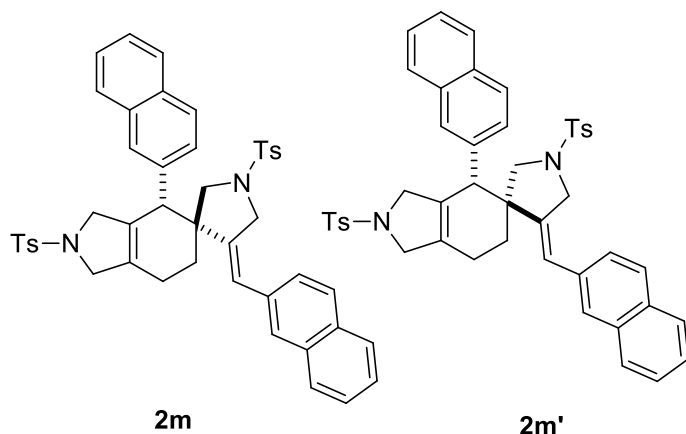
Compound **2l** (55.0 mg, 0.068 mmol, 45% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1l** (0.3 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.69 (dd, *J* = 8.1, 4.0 Hz, 4H), 7.44–7.17 (m, 8H), 6.60 (dd, *J* = 10.9, 8.4 Hz, 4H), 4.98 (s, 1H), 4.30 (dd, *J* = 15.0, 2.3 Hz, 1H), 4.17 (q, *J* = 12.8, 12.0 Hz, 2H), 3.83–3.74 (m, 3H), 3.54 (d, *J* = 9.3 Hz, 1H), 3.18 (s, 1H), 2.74 (d, *J* = 9.3 Hz, 1H), 2.47 (s, 3H), 2.41 (s, 3H), 2.27–2.16 (m, 1H), 2.07–1.83 (m, 2H), 1.34 (dd, *J* = 13.0, 4.9 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 144.2 (Cq), 143.7 (Cq), 140.5 (Cq), 137.6 (Cq), 134.7 (Cq), 134.2 (Cq), 132.6 (Cq), 131.61 (Cq), 131.6 (4CH), 131.1 (2CH), 130.4 (Cq), 130.0 (4CH), 129.4 (2CH), 127.7 (2CH), 127.4 (2CH), 124.1 (CH), 121.2 (Cq), 121.2 (Cq), 57.5 (CH₂), 57.0 (CH₂), 56.2 (CH₂), 51.2 (CH₂), 50.4 (Cq), 46.6 (CH), 26.0 (CH₂), 21.65 (CH₃), 21.61 (CH₃), 21.2 (CH₂) (ESI)-HRMS calcd for C₃₈H₃₇Br₂N₂O₄S₂ [M + H]⁺ 809.0561, found 809.0569.

(3'R,4S,Z)-4'-(4-Bromobenzylidene)-4-(4-bromophenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2I').



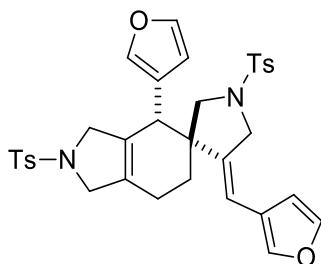
Compound **2I'** (35.0 mg, 0.043 mmol, 29% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1I** (0.3 mmol); ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, *J* = 7.0 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.44–7.30 (m, 7H), 6.89 (d, *J* = 7.0 Hz, 2H), 6.78 (d, *J* = 7.2 Hz, 1H), 6.03 (s, 1H), 4.26–4.06 (m, 3H), 3.97–3.76 (m, 2H), 3.63 (d, *J* = 14.8 Hz, 1H), 3.24 (s, 1H), 2.85 (d, *J* = 8.6 Hz, 1H), 2.69 (d, *J* = 9.6 Hz, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 2.16 (d, *J* = 17.8 Hz, 1H), 1.99 (d, *J* = 17.7 Hz, 1H), 1.85 (d, *J* = 13.5 Hz, 1H), 1.80–1.68 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 143.9 (Cq), 143.7 (Cq), 143.1 (Cq), 136.9 (Cq), 134.8 (Cq), 133.9 (Cq), 133.2 (Cq), 132.6 (Cq), 131.8 (4CH), 130.3 (Cq), 129.9 (2CH), 129.8 (4CH), 129.8 (2CH), 127.6 (2CH), 127.5 (2CH), 121.8 (Cq), 121.4 (Cq), 121.2 (CH), 57.2 (CH₂), 55.8 (CH₂), 55.5 (CH₂), 50.8 (CH₂), 49.3 (Cq), 47.3 (CH), 28.4 (CH₂), 21.63 (CH₃), 21.62 (CH₃), 20.7 (CH₂). (ESI)-HRMS calcd for C₃₈H₃₇Br₂N₂O₄S₂ [M + H]⁺ 809.0561, found 809.0559.

(4S,5S,Z)-4'-(Naphthalen-1-ylmethylene)-4-(naphthalen-2-yl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] and **(4S,5R,Z)-4'-(Naphthalen-1-ylmethylene)-4-(naphthalen-2-yl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine]** (**2m/2m'**).



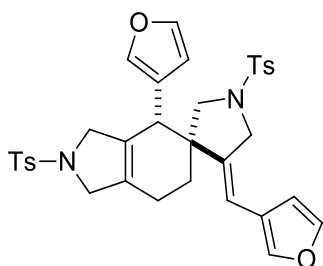
Compounds **2m/2m'** (52.0 mg, 0.069 mmol, 69% yield, ¹H NMR ratio 80:20) were obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1m** (0.3 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.86–7.81 (m, 2H), 7.75–7.69 (m, 7H), 7.65–7.63 (m, 2H), 7.61–7.56 (m, 5H), 7.54–7.51 (m, 3H), 7.47–7.45 (m, 3H), 7.42–7.40 (m, 5H), 7.34–7.32 (m, 5H), 7.27–7.25 (m, 2H), 7.22 (brs, 2H), 7.18–7.16 (m, 2H), 7.09–7.07 (m, 2H), 6.96–6.94 (m, 2H), 6.90 (brs, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.29 (s, 1H), 5.13 (s, 1H), 4.56 (dd, *J* = 14.8, 2.6 Hz, 1H), 4.42 (dd, *J* = 14.9, 2.6 Hz, 1H), 4.31–4.20 (m, 4H), 3.99–3.95 (m, 2H), 3.91–3.79 (m, 4H), 3.66 (d, *J* = 9.2 Hz, 2H), 3.50 (s, 1H), 3.44 (s, 1H), 2.96 (d, *J* = 9.6 Hz, 1H), 2.85 (d, *J* = 9.2 Hz, 2H), 2.66 (d, *J* = 9.7 Hz, 1H), 2.48 (s, 3H), 2.40 (s, 6H), 2.36 (s, 3H), 2.33–2.28 (m, 2H), 2.13–2.08 (m, 3H), 1.91–1.88 (m, 1H), 1.43–1.41 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 144.0, 143.6, 143.5, 142.7, 140.2, 136.2, 135.7, 134.3, 133.9, 133.6, 133.5, 133.3, 133.2, 133.0, 133.0, 132.9, 132.8, 132.8, 132.7, 132.6, 132.4, 132.1, 131.3, 131.0, 130.8, 130.0, 129.9, 129.8, 129.6, 128.2, 128.1, 127.9, 127.8, 127.7, 127.7, 127.7, 127.5, 127.5, 127.5, 127.4, 126.8, 126.6, 126.4, 126.4, 126.3, 126.2, 126.1, 126.0, 125.9, 125.7, 125.1, 122.3, 60.4, 57.8, 57.4, 57.1, 56.5, 56.2, 56.1, 51.4, 50.9, 50.6, 49.6, 47.4, 26.3, 21.6, 21.6, 21.5, 21.4, 21.1, 20.7. (ESI)-HRMS calcd for C₄₆H₄₃N₂O₄S₂ [M + H]⁺ 751.2664, found 751.2671.

(4S,5R,Z)-4-(Furan-3-yl)-4'-(furan-3-ylmethylene)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2n).



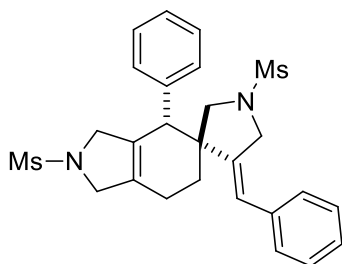
Compound **2n** (31.5 mg, 0.050 mmol, 50% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1n** (0.2 mmol); ¹H NMR (300 MHz, CDCl₃) δ = 7.70 (dd, *J* = 8.2, 2.7 Hz, 4H), 7.42–7.26 (m, 5H), 7.16 (d, *J* = 6.9 Hz, 2H), 6.74 (s, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 5.82 (d, *J* = 1.8 Hz, 1H), 5.26 (s, 1H), 4.19–4.11 (m, 3H), 3.97–3.93 (m, 1H), 3.84–3.79 (m, 2H), 3.48 (d, *J* = 9.2 Hz, 1H), 3.09 (s, 1H), 2.74 (d, *J* = 9.2 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.17–1.83 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ = 144.0 (Cq), 143.6 (Cq), 143.3 (Cq), 142.4 (Cq), 140.6 (Cq), 140.6 (Cq), 138.4 (Cq), 134.4 (Cq), 132.7 (Cq), 131.2 (CH), 130.1 (CH), 129.9 (2CH), 129.8 (2CH), 127.6 (2CH), 127.4 (2CH), 123.0 (CH), 121.8 (CH), 114.7 (CH), 111.3 (CH), 109.8 (CH), 57.0 (CH₂), 56.9 (CH₂), 56.2 (CH₂), 51.3 (Cq), 49.5 (CH₂), 37.8 (CH₂), 29.7 (CH), 26.3 (CH₂), 21.5 (CH₃), 21.5 (CH₃). (ESI)-HRMS calcd for C₃₄H₃₄N₂NaO₆S₂ [M + Na]⁺ 653.1756, found 653.1753.

(4S,5S,Z)-4-(Furan-3-yl)-4'-(furan-3-ylmethylene)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2n').



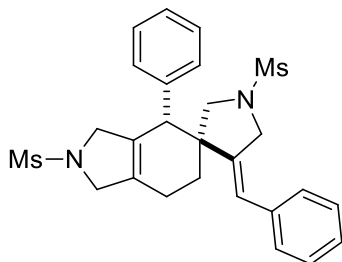
Compound **2n'** (18.5 mg, 0.029 mmol, 29% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1n** (0.2 mmol); **2n'** ¹H NMR (300 MHz, CDCl₃) δ = 7.71–7.60 (m, 5H), 7.39–7.31 (m, 5H), 7.17 (s, 1H), 6.94 (s, 1H), 6.20 (s, 1H), 5.98 (s, 1H), 5.79 (s, 1H), 4.37–4.34 (m, 2H), 4.13–4.07 (m, 4H), 3.94 (m, 2H), 3.13 (m, 1H), 2.90–2.82 (m, 2H), 2.46 (s, 3H), 2.42 (s, 3H), 1.95–1.80 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ = 143.8, 143.6, 143.4, 143.3, 140.9, 140.4, 132.2, 132.1, 129.8, 129.7, 128.6, 128.4, 127.7, 127.5, 122.4, 122.0, 111.7, 110.5, 110.0, 57.2, 56.7, 56.0, 51.8, 51.4, 48.6, 38.4, 31.9, 25.8, 22.7, 21.5. (ESI)-HRMS calcd for C₃₄H₃₄N₂NaO₆S₂ [M + Na]⁺ 653.1756, found 653.1765.

(4S,5R)-4'-((Z)-Benzylidene)-1',2-bis(methylsulfonyl)-4-phenyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2o).



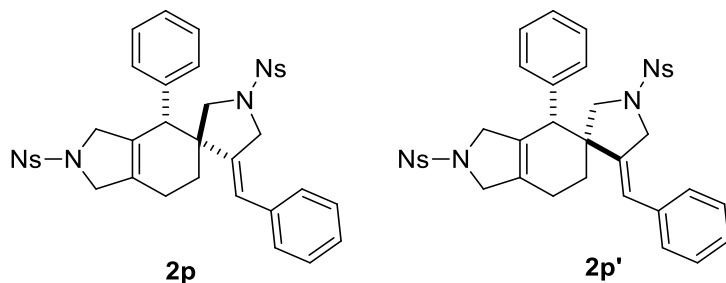
Compound **2o** (23.7 mg, 0.046 mmol, 48% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1o** (0.2 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.41–7.37 (m, 2H), 7.33–7.28 (m, 4H), 7.19–7.15 (m, 4H), 6.35 (s, 1H), 4.41 (dd, *J* = 14.8, 2.7 Hz, 1H), 4.22 (d, *J* = 17.0 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 1H), 4.05–3.86 (m, 4H), 3.48 (brs, 1H), 3.14 (d, *J* = 9.7 Hz, 1H), 2.79 (d, *J* = 12.2 Hz, 1H), 2.80 (s, 3H), 2.69 (s, 3H), 2.08–1.93 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 142.2 (Cq), 138.2 (Cq), 136.0 (Cq), 132.7 (Cq), 131.1 (Cq), 128.8 (4CH), 128.7 (2CH), 128.4 (2CH), 127.9 (CH), 127.6 (CH), 122.5 (CH), 57.1 (CH₂), 55.9 (CH₂), 50.7 (CH₂), 49.6 (CH₂), 47.9 (Cq), 35.5 (CH₃), 34.8 (CH₃), 28.3 (CH₂), 20.7 (CH₂). (ESI)-HRMS calcd for C₂₆H₃₀KN₂O₄S₂ [M + Na]⁺ 537.1284, found 537.1277.

(4S,5S)-4'-((Z)-Benzylidene)-1',2-bis(methylsulfonyl)-4-phenyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2o').



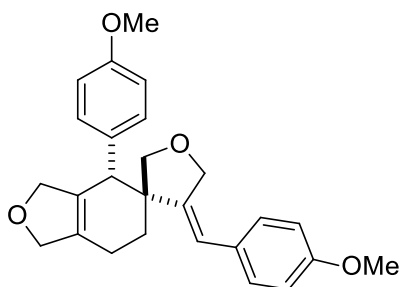
Compound **2o'** (10.1 mg, 0.020 mmol, 20% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1o** (0.2 mmol); ¹H NMR (300 MHz, CDCl₃) δ = 7.29–7.18 (m, 6H), 7.06–7.04 (m, 2H), 6.89–6.83 (m, 2H), 5.32 (brs, 1H), 4.52 (dd, *J* = 14.9, 2.7 Hz, 1H), 4.32–4.06 (m, 4H), 3.96 (brs, 2H), 3.75 (d, *J* = 9.1 Hz, 1H), 3.57 (brs, 1H), 3.08 (d, *J* = 9.2 Hz, 1H), 2.90 (s, 3H), 2.85 (s, 3H), 2.44–2.12 (m, 3H), 1.63–1.58 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 139.7 (Cq), 138.4 (Cq), 136.0 (Cq), 131.2 (Cq), 130.9 (Cq), 128.8 (2CH), 128.3 (2CH), 128.2 (2CH), 127.9 (2CH), 127.4 (CH), 127.2 (CH), 125.0 (CH), 57.5 (CH₂), 57.0 (CH₂), 56.4 (CH₂), 51.3 (CH₂), 50.6 (Cq), 47.2 (CH), 35.0 (CH₃), 34.9 (CH₃), 26.1 (CH₂), 21.3 (CH₂). (ESI)-HRMS calcd for C₂₆H₃₀KN₂O₄S₂ [M + Na]⁺ 537.1284, found 537.1273.

(3'R,4S,Z)-4'-Benzylidene-1',2-bis((4-nitrophenyl)sulfonyl)-4-phenyl-1,2,3,4,6,7-hexahydrospiro[isindole-5,3'-pyrrolidine] and **(3'S,4S,Z)-4'-Benzylidene-1',2-bis((4-nitrophenyl)sulfonyl)-4-phenyl-1,2,3,4,6,7-hexahydrospiro[isindole-5,3'-pyrrolidine]** (**2p/2p'**).



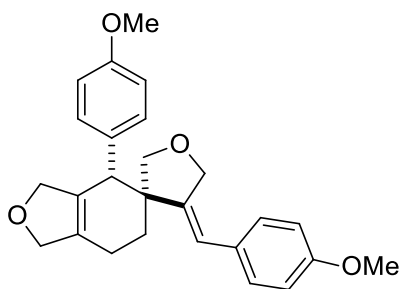
Compounds **2p/2p'** (41.3 mg, 0.058 mmol, 65% yield, $^1\text{H NMR}$ ratio 67:33) were obtained as a white solid (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1p** (0.178 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.46–8.29 (m, 8H), 8.06–7.94 (m, 6H), 7.84 (d, J = 8.8 Hz, 2H), 7.41–7.15 (m, 14H), 7.01 (d, J = 7.3 Hz, 1H), 6.97 (d, J = 7.0 Hz, 1H), 6.90–6.84 (m, 2H), 6.76–6.69 (m, 2H), 6.12 (s, 1H), 5.16 (s, 1H), 4.52 (dd, J = 14.8, 2.6 Hz, 1H), 4.36–4.09 (m, 5H), 3.95 (s, 4H), 3.86–3.73 (m, 2H), 3.66 (d, J = 9.0 Hz, 1H), 3.43 (s, 1H), 3.32 (s, 1H), 2.98 (d, J = 9.7 Hz, 1H), 2.76–2.69 (m, 2H), 2.31 (d, J = 12.0 Hz, 1H), 2.24–2.03 (m, 4H), 1.89–1.79 (m, 2H), 1.46–1.33 (m, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 150.3 (Cq), 150.3 (Cq), 150.2 (Cq), 150.1 (Cq), 143.2 (Cq), 142.9 (Cq), 142.1 (Cq), 141.8 (Cq) (Cq), 141.1 (Cq), 138.6 (Cq), 138.0 (Cq), 137.5 (Cq), 135.7 (Cq), 135.6 (Cq), 132.4 (Cq), 131.1 (Cq), 130.9 (Cq), 130.8 (Cq), 128.8 (2 + 2CH), 128.7 (2CH), 128.48 (4 + 2CH), 128.46 (2CH), 128.4 (2CH), 128.3 (4CH), 128.2 (2CH), 128.1 (CH), 127.9 (CH), 127.8 (2CH), 127.7 (CH), 127.4 (CH), 125.4 (CH), 124.63 (2CH), 124.56 (2CH), 124.5 (2CH), 124.4 (2CH), 122.8 (CH), 57.6 (CH₂), 57.3 (CH₂), 57.1 (CH₂), 56.6 (CH₂), 56.0 (CH₂), 55.8 (CH₂), 51.2 (CH₂), 50.7 (Cq), 50.4 (CH₂), 49.3 (Cq), 47.7 (CH), 47.2 (CH), 28.2 (CH₂), 25.9 (CH₂), 21.2 (CH₂), 20.7 (CH₂). (**ESI**)-**HRMS** calcd for $\text{C}_{36}\text{H}_{32}\text{N}_4\text{NaO}_8\text{S}_2$ $[\text{M} + \text{Na}]^+$ 735.1559, found 735.1568.

(3'R,4S,Z)-4'-Benzylidene-1',2-bis((4-methoxyphenyl)sulfonyl)-4-phenyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] (2q).



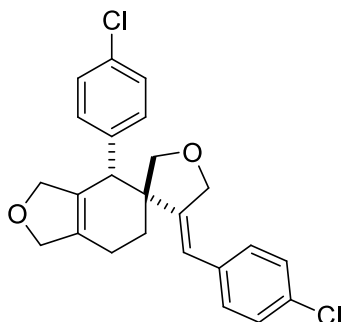
Compound **2q** (21.8 mg, 0.054 mmol, 36% yield) was obtained as a colorless oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1q** (0.3 mmol); **¹H NMR** (400 MHz, CDCl₃) δ = 6.92 (d, J = 8.0 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.74 (m, 4H), 4.94 (s, 1H), 4.81 (d, J = 14.3 Hz, 1H), 4.70 (brs, 2H), 4.62 (d, J = 14.3, 2.6 Hz, 1H), 4.44–4.40 (m, 2H), 4.06 (d, J = 8.3 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.61 (d, J = 8.4 Hz, 1H), 3.42 (brs, 1H), 2.31 (d, J = 11.5 Hz, 1H), 2.09 (d, J = 10.4 Hz, 2H), 1.52 (d, J = 8.2 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 158.5 (Cq), 158.3 (Cq), 142.1 (Cq), 132.7 (Cq), 132.1 (Cq), 131.8 (Cq), 130.6 (2CH), 130.1 (Cq), 129.2 (2CH), 122.4 (CH), 113.8 (2CH), 113.1 (2CH), 78.3 (CH₂), 77.5 (2CH₂), 71.5 (CH₂), 55.4 (CH₃), 55.4 (CH₃), 51.5 (Cspiro), 45.4 (CH), 26.3 (CH₂), 20.5 (CH₂). **(ESI)- HRMS** calcd C₂₆H₂₉O₄ [M + H]⁺ 405.2066, found 405.2063.

(3'S,4S,Z)-4'-Benzylidene-1',2-bis((4-methoxyphenyl)sulfonyl)-4-phenyl-1,2,3,4,6,7-hexahydrospiro[indole-5,3'-pyrrolidine] (2q').



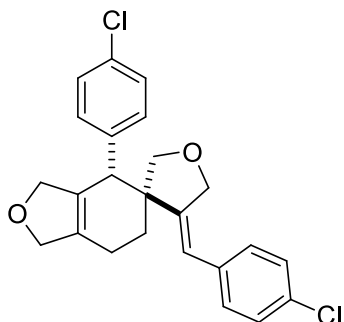
Compound **2q'** (11.8 mg, 0.029 mmol, 19% yield) was obtained as a yellowish solid (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1q** (0.3 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.08 (dd, *J* = 8.7, 2.8 Hz, 4H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 6.25 (s, 1H) 4.80–4.59 (m, 4H), 4.48–4.44 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.66 (d, *J* = 8.8 Hz, 1H), 3.42 (s, 1H) 3.13 (d, *J* = 8.8 Hz, 1H), 2.25–2.10 (brs, 2H), 1.93–1.86 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 158.8 (Cq), 158.5 (Cq), 145.1 (Cq), 133.6 (Cq), 132.6 (Cq), 131.6 (Cq), 130.1 (Cq, 2CH), 129.6 (2CH), 119.2 (CH), 114.1 (2CH), 113.7 (2CH), 77.7 (CH₂) 77.4 (CH₂), 76.6 (CH₂), 71.1 (CH₂), 55.5 (CH₃), 55.3 (CH₃), 50.1 (Cq), 45.7 (CH), 28.4 (CH₂), 19.5 (CH₂). (ESI)-HRMS calcd C₂₆H₂₉O₄ [M + H]⁺ 405.2066, found 405.2058.

(3*S*,4'*S*,*Z*)-4-(4-Chlorobenzylidene)-4'-(4-chlorophenyl)-3',4,4',5,6',7'-hexahydro-1'*H*,2*H*-spiro[furan-3,5'-isobenzofuran] (2*r*).



Compound **2r** (56.7 mg, 0.137 mmol, 46% yield) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1r** (0.3 mmol); ¹**H NMR** (400 MHz, CDCl₃) δ = 7.31–7.14 (m, 4H), 6.93 (d, *J* = 7.7 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 2H), 4.93 (s, 1H), 4.84–4.74 (m, 1H), 4.70 (s, 2H), 4.66–4.54 (m, 1H), 4.50–4.29 (m, 2H), 4.07 (d, *J* = 8.4 Hz, 1H), 3.61 (d, *J* = 8.5 Hz, 1H), 3.45 (s, 1H), 2.33 (d, *J* = 11.7 Hz, 1H), 2.20–1.98 (m, 2H), 1.61–1.49 (m, 1H). ¹³**C NMR** (101 MHz, CDCl₃) δ = 144.8 (Cq), 138.0 (Cq), 135.2 (Cq), 132.8 (Cq), 132.7 (Cq), 132.5 (Cq), 131.8 (Cq), 130.8 (2CH), 129.0 (2CH), 128.6 (2CH), 127.9 (2CH), 121.9 (CH), 78.1 (CH₂), 77.3 (CH₂), 76.8 (CH₂), 71.3 (CH₂), 51.5 (Cq), 45.5 (CH), 26.0 (CH₂), 20.3 (CH₂). **(ESI)-HRMS** calcd for C₂₄H₂₃Cl₂O₂ [M + H]⁺ 413.1075, found 413.1065.

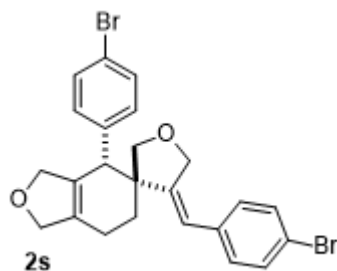
(3R,4'S,Z)-4-(4-Chlorobenzylidene)-4'-(4-chlorophenyl)-3',4,4',5,6',7'-hexahydro-1'H,2H-spiro[furan-3,5'-isobenzofuran] (2r').



Compound **2r'** (19.9 mg, 0.048 mmol, 16% yield) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1r** (0.3 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.35–7.22 (m, 4H), 7.10 (d, *J* = 7.7 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.27 (s, 1H), 4.75–4.55 (m, 2H), 4.50–4.36 (m, 2H), 3.67 (d, *J* = 8.9 Hz, 1H), 3.45 (s, 1H), 3.16 (d, *J* = 8.8 Hz, 1H), 2.28–2.06 (m, 2H), 1.99–1.82 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 147.8 (Cq), 137.6 (Cq), 135.4 (Cq), 134.3 (Cq), 133.2 (Cq), 132.7 (Cq), 131.7 (Cq), 130.3 (2CH), 129.4 (2CH), 128.8 (2CH), 128.5 (2CH), 118.9 (CH), 77.5 (CH₂), 76.2 (CH₂), 76.0 (CH₂), 70.8 (CH₂), 50.1 (Cq), 46.1 (CH), 28.6 (CH₂), 19.4 (CH₂). (ESI)-HRMS calcd for C₂₄H₂₃Cl₂O₂ [M + H]⁺ 413.1075, found 413.1079.

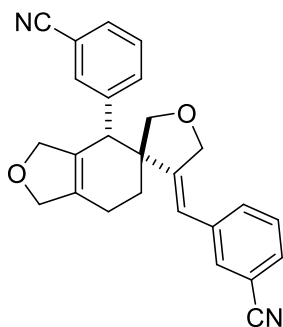
(3*S*,4'*S*,*Z*)-4-(4-Bromobenzylidene)-4'-(4-bromophenyl)-1'*H*,2*H*-spiro[furan-3,5'-isobenzofuran] (**2s**).

3',4,4',5,6',7'-hexahydro-



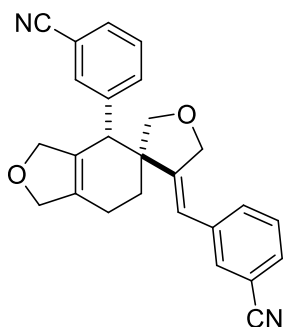
Compound **2s** (16.0 mg, 0.032 mmol, 21% yield) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1s** (0.3 mmol); the low amount of **2s'** did not allow us to fully characterize it. From diagnostic vinyl resonances of the crude spectrum, the ¹H NMR ratio of **2s/2s'** was 63:37. ¹H NMR (400 MHz, CDCl₃) δ = 7.39 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 6.9 Hz, 2H), 6.64 (d, *J* = 8.1 Hz, 2H), 4.90 (brs, 1H), 4.77 (dd, *J* = 14.3, 1H), 4.70 (brs, 2H), 4.59 (d, *J* = 14.3, 1H), 4.43–4.38 (m, 2H), 4.07 (d, *J* = 8.4 Hz, 1H), 3.61 (d, *J* = 8.4 Hz, 1H), 3.43 (brs, 1H), 2.34–2.31 (m, 1H), 2.11–2.01 (m, 2H), 1.57–1.53 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 145.0 (Cq), 138.5 (Cq), 135.8 (Cq), 133.0 (Cq), 131.7 (Cq), 131.5(4CH), 130.8 (2CH), 129.3 (2CH), 122.0 (Cq), 120.8 (Cq), 120.6 (Cq), 78.1 (CH₂), 77.2 (CH₂), 76.8 (CH₂), 71.4 (CH₂), 51.4 (Cq), 45.6 (CH), 26.0 (CH₂), 20.3 (CH₂). (ESI)-HRMS calcd C₂₄H₂₃Br₂O₂ [M + H]⁺ 503.0065, found 503.0071.

3-((3S,4'S,Z)-4-(3-Cyanobenzylidene)-3',4,4',5,6',7'-hexahydro-1'H,2H-spiro[furan-3,5'-isobenzofuran]-4'-yl)benzonitrile (2t).



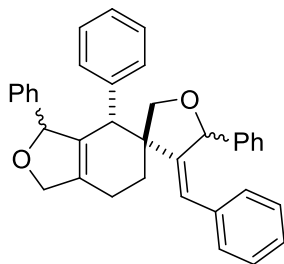
Compound **2t** (24.4 mg, 0.062 mmol, 41% yield) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1t** (0.3 mmol); **¹H NMR** (400 MHz, CDCl₃) δ = 7.52 (d, J = 7.6, 1H), 7.46 (d, J = 7.6, 1H), 7.43–7.28 (m, 3H), 7.25–7.19 (m, 1H), 7.05 (s, 1H), 6.97 (d, J = 7.8, 1H), 4.93 (t, J = 2.7 Hz, 1H), 4.85 (dd, J = 14.6, 2.6 Hz, 1H), 4.79–4.68 (m, 2H), 4.61 (dd, J = 14.7, 2.7 Hz, 1H), 4.51–4.41 (m, 1H), 4.34 (ddt, J = 11.7, 5.5, 2.8 Hz, 1H), 4.11 (d, J = 8.6 Hz, 1H), 3.63 (d, J = 8.6 Hz, 1H), 3.53 (s, 1H), 2.44–2.34 (m, 1H), 2.22–1.98 (m, 2H), 1.59 (dd, J = 12.9, 5.2 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ = 147.2 (Cq), 141.1 (Cq), 137.4 (Cq), 133.9 (Cq), 131.8 (CH), 130.9 (CH), 130.8 (Cq), 130.7 (CH), 130.4 (CH), 129.4 (2CH), 128.6 (CH), 128.5 (Cq), 121.2 (CH), 118.68 (Cq), 118.5 (Cq), 112.8 (Cq), 112.1 (Cq), 77.9 (CH₂), 77.3 (CH₂), 76.6 (CH₂), 71.1 (CH₂), 51.7 (Cq), 45.6 (CH), 25.8 (CH₂), 20.2 (CH₂). **(ESI)-HRMS** calcd for C₂₆H₂₂N₂NaO₂ [M + Na]⁺ 417.1579, found 417.1585.

3-((3R,4'S,Z)-4-(3-Cyanobenzylidene)-3',4,4',5,6',7'-hexahydro-1'H,2H-spiro[furan-3,5'-isobenzofuran]-4'-yl)benzonitrile (2t').



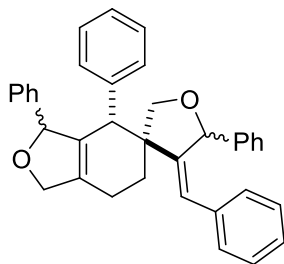
Compound **2t'** (7.5 mg, 0.019 mmol, 13% yield) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1t** (0.3 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.61–7.32 (m, 8H), 6.32 (t, J = 2.6 Hz, 1H), 4.81–4.63 (m, 3H), 4.52–4.28 (m, 3H), 3.68 (d, J = 9.0 Hz, 1H), 3.52 (s, 1H), 3.16 (d, J = 9.0 Hz, 1H), 2.36–2.23 (m, 1H), 2.23–2.08 (m, 1H), 2.03–1.96 (m, 1H), 1.87 (ddd, J = 13.8, 8.5, 5.4 Hz, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 150.0 (Cq), 140.6 (Cq), 137.9 (Cq), 135.4 (CH), 132.3 (2CH), 131.6 (CH), 131.2 (CH), 130.8 (Cq), 130.4 (CH), 129.5 (2CH), 129.3 (CH), 118.61 (Cq), 118.58 (Cq), 118.4 (CH), 113.0 (Cq), 112.7 (Cq), 77.5 (CH_2), 76.0 (CH_2), 75.9 (CH_2), 70.7 (CH_2), 50.2 (Cq), 46.4 (CH), 29.7 (CH_2), 19.3 (CH_2). (ESI)-**HRMS** calcd for $\text{C}_{26}\text{H}_{22}\text{N}_2\text{NaO}_2$ [$\text{M} + \text{Na}$] $^+$ 417.1579, found 417.1574.

(3*S*,4'*R*,*Z*)-4-Benzylidene-3',4',5-triphenyl-3',4,4',5,6',7'-hexahydro-1'*H*,2*H*-spiro[furan-3,5'-isobenzofuran] (2u).



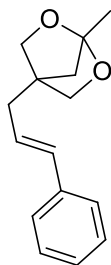
Compound **2u** (23.6 mg, 0.047 mmol, 32% yield) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure from **1u** (0.3 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.35–7.16 (m, 13H), 7.12–7.06 (m, 2H), 7.01–6.93 (m, 3H), 6.54–6.49 (m, 2H), 5.83 (d, *J* = 1.9 Hz, 1H), 5.47–5.34 (m, 1H), 5.06–4.94 (m, 2H), 4.91–4.82 (m, 1H), 3.64 (d, *J* = 8.6 Hz, 1H), 3.56 (d, *J* = 8.7 Hz, 1H), 3.10 (s, 1H), 2.43 (d, *J* = 15.2 Hz, 1H), 2.35–2.15 (m, 2H), 1.79 (dd, *J* = 13.1, 5.4 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 143.9 (Cq), 141.4 (Cq), 139.2 (Cq), 139.0 (Cq), 136.2 (Cq), 136.0 (Cq), 132.3 (Cq), 128.6 (2CH), 128.5 (3CH), 128.3 (2CH), 128.3 (2CH), 128.0 (CH), 128.0 (CH), 127.8 (3CH), 126.9 (CH), 126.4 (2CH), 126.3 (2CH), 89.0 (CH), 83.0 (CH), 77.5 (CH₂), 75.3 (CH₂), 51.9 (Cq), 47.4 (CH), 26.8 (CH₂), 20.4 (CH₂). (ESI)-HRMS calcd for C₃₆H₃₃O₂ [M + H]⁺ 497.2481, found 497.2486.

(3R,4'R,Z)-4-Benzylidene-3',4',5-triphenyl-3',4,4',5,6',7'-hexahydro-1'H,2H-spiro[furan-3,5'-isobenzofuran] (2u').



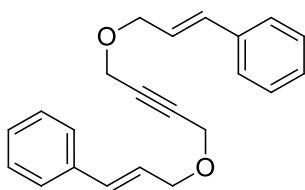
Compound **2u'** (18.5 mg, 0.037 mmol, 25% yield) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure GP-1 from 1u (0.3 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.41–7.05 (m, 18H), 6.82 (dd, *J* = 7.6, 1.8 Hz, 2H), 6.22 (d, *J* = 2.2 Hz, 1H), 5.67 (d, *J* = 1.8 Hz, 1H), 5.44 (dt, *J* = 5.6, 2.8 Hz, 1H), 5.08 (ddd, *J* = 12.2, 5.5, 2.9 Hz, 1H), 4.91 (d, *J* = 12.3 Hz, 1H), 3.64 (d, *J* = 8.9 Hz, 1H), 3.16 (s, 1H), 3.03 (d, *J* = 8.8 Hz, 1H), 2.36–2.26 (m, 2H), 1.92 (t, *J* = 6.1 Hz, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 146.6 (Cq), 142.1 (Cq), 139.6 (Cq), 139.1 (Cq), 135.9 (Cq), 135.7 (Cq), 133.6 (Cq), 129.0 (2CH), 128.5 (4CH), 128.4 (4CH), 128.1 (2CH), 127.9 (CH), 127.7 (CH), 127.5 (2CH), 127.3 (CH), 126.8 (CH), 126.0 (2CH), 123.3 (CH), 88.3 (CH), 82.6 (CH), 77.9 (CH₂), 75.9 (CH₂), 50.3 (Cq), 46.2 (CH), 26.9 (CH₂), 19.5 (CH₂). (ESI)-HRMS calcd for C₃₆H₃₃O₂ [M + H]⁺ 497.2481, found 497.2475.

4-Cinnamyl-1-methyl-2,6-dioxabicyclo[2.2.1]heptane (**2v'**).



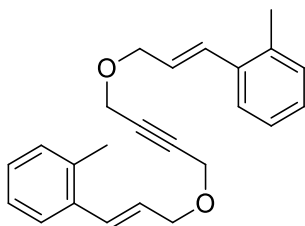
Compound **2v'** (29.0 mg, 0.13 mmol, 42% yield) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-1** from **1v** (0.3 mmol); spectroscopic data correspond to the literature.⁷⁴ **¹H NMR** (400 MHz, CDCl₃) δ = 7.40–7.20 (m, 5H), 6.44 (d, J = 15.7 Hz, 1H), 6.17–6.14 (m, 1H), 3.82 (d, J = 3.8 Hz, 4H), 2.50 (d, J = 7.7 Hz, 2H), 1.76 (s, 2H), 1.56 (3H). **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ = 137.0 (Cq), 133.1 (CH), 128.7 (2CH), 127.6 (CH), 126.2 (2CH), 124.9 (CH), 108.6 (Cq), 76.4 (2CH₂), 49.4 (Cq), 44.3 (CH₂), 32.1 (CH₂), 18.1 (CH₃).

1,4-Bis(cinnamyloxy)but-2-yne (**3a**).



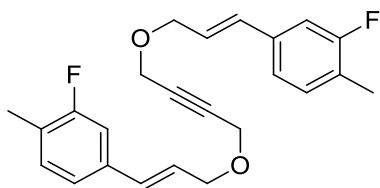
Following the literature procedure, **3a** was isolated (silica gel, n-hexanes/EtOAc, gradient) as a white solid. (300 mg, 0.94 mmol, 52%). The spectral data for this compound correspond to the literature.⁷⁶ **¹H NMR** (400 MHz, CDCl₃): δ = 7.35–7.17 (m, 10H), 6.60 (d, J = 15.86 Hz, 2H), 6.24 (dtd, J = 15.89, 6.17, 1.83 Hz, 2H), 4.22 (d, J = 1.53 Hz, 4H), 4.20 (d, J = 6.17, 4H).

1,4-Bis(((E)-3-(o-tolyl)allyl)oxy)but-2-yne (3b).



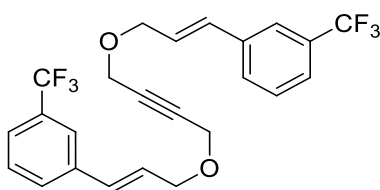
Following **GP-2a**, product **3b** was isolated (silica gel, n-hexanes/EtOAc, gradient) as a white solid (307 mg, 0.89 mmol, 34%). The spectral data for this compound correspond to the literature.⁶⁶ **¹H NMR** (400 MHz, CDCl₃) δ = 7.49–7.46 (m, 2H), 7.21–7.18 (m, 6H), 6.89 (d, J = 15.7 Hz, 2H), 6.24–6.16 (m, 2H), 4.31–4.28 (m, 8H), 2.37 (s, 6H).

1,4-Bis(((E)-3-(3-fluoro-4-methylphenyl)allyl)oxy)but-2-yne (3c).



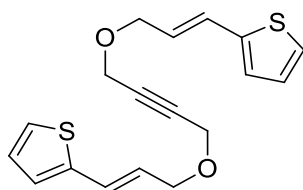
Following **GP-2a**, product **3c** was isolated (silica gel, n-hexanes/ EtOAc, gradient) as a white solid (222 mg, 0.58 mmol, 25%). The spectral data for this compound correspond to the literature.⁶⁶ **¹H NMR** (400 MHz, CDCl₃) δ = 7.13–7.09 (m, 2H), 7.05–7.03 (m, 4H), 6.57 (d, J = 15.9 Hz, 2H), 6.24 (dt, J = 16.0, 6.1 Hz, 2H), 4.27 (s, 4H), 4.23 (dd, J = 6.0, 1.4 Hz, 4H) 2.25 (s, 6H).

1,4-Bis(((E)-3-(3-(trifluoromethyl)phenyl)allyl)oxy)but-2-yn (3d).



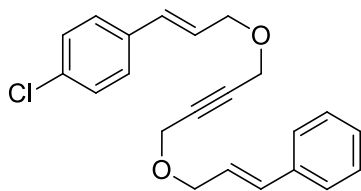
Following **GP-2a**, product **3d** was isolated (silica gel, n-hexanes/ EtOAc, gradient) as a colorless oil (222 mg, 0.49 mmol, 25%). The spectral data for this compound correspond to the literature.⁶⁶ **¹H NMR** (400 MHz, CDCl₃) δ = 7.62 (s, 2H), 7.59–7.36 (m, 6H), 6.68 (d, J = 15.9 Hz, 2H), 6.36 (dt, J = 16.0, 5.9 Hz, 2H), 4.28 (s, 4H), 4.27–4.23 (m, 4H).

1,4-Bis(((E)-3-(thiophen-2-yl)allyl)oxy)but-2-yne (3e).



Following **GP-2a**, product **3e** was isolated (silica gel, n-hexanes/ EtOAc, gradient) as a yellow oil (227 mg, 0.69 mmol, 50%). The spectral data for this compound correspond to the literature.⁶⁶ **¹H NMR** (300 MHz, CDCl₃) δ = 7.19–7.13 (m, 2H), 7.01–6.89 (m, 4H), 6.77 (d, J = 15.6 Hz, 2H), 6.11 (dt, J = 15.7, 6.2 Hz, 2H), 4.25 (s, 4H), 4.20 (dd, J = 6.2, 1.4 Hz, 4H).

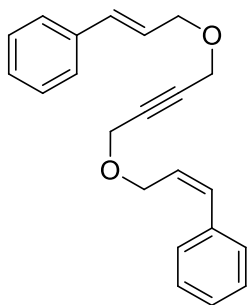
1-Chloro-4-((E)-3-((4-(cinnamyloxy)but-2-yn-1-yl)oxy)prop1-en-1-yl)benzene (3f).



Compound **3f** (129 mg, 0.37 mmol, 54% yield) was prepared adapting a literature procedure ⁶³ and obtained (silica gel, n-hexanes/EtOAc, gradient) as a colorless oil. ¹ **H NMR** (400 MHz, CDCl₃) δ = 7.44–7.39 (m, 2H), 7.37–7.23 (m, 7H), 6.71–6.58 (m, 2H), 6.36–6.23 (m, 2H), 4.29 (s, 4H), 4.28–4.24 (m, 4H). ¹³**C NMR** (101 MHz, CDCl₃) δ = 136.5 (Cq), 135.1 (Cq), 133.5 (Cq), 133.3 (CH), 131.8 (CH), 128.8 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 126.5 (CH), 125.9 (CH), 125.1 (CH), 82.6 (Cq), 82.4 (Cq), 70.3 (CH₂), 70.1 (CH₂), 57.6 (CH₂), 57.4 (CH₂). **(ESI)-HRMS** calcd for C₂₂H₂₁ClNaO₂ [M + Na]⁺ 375.1230, found 375.1223.

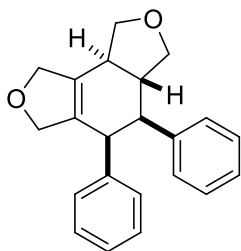
⁶³ Lanzi, M.; Cañeque, T.; Marchio, L.; Maggi, R.; Bigi, F.; Malacria, M.; Maestri, G. Alternative Routes to Tricyclic Cyclohexenes with Trinuclear Palladium Complexes. *ACS Catal.* **2018**, 8, 144.

1-(Cinnamyloxy)-4-(((Z)-3-phenylallyl)oxy)but-2-yne (3g).



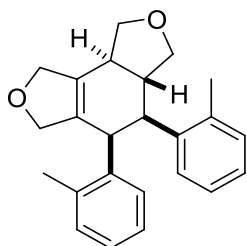
Compound **3g** (98.6 mg, 0.31 mmol, 56% yield) was prepared adapting a literature procedure ⁶³ and obtained (silica gel, n-hexanes/ EtOAc, gradient) as a colorless oil. ¹ **H NMR** (400 MHz, CDCl₃) δ = 7.45–7.23 (m, 10H), 6.71–6.60 (m, 2H), 6.28 (dt, J = 15.9, 6.2 Hz, 1H), 5.88 (dt, J = 12.3, 6.4 Hz, 1H), 4.38 (d, J = 6.5 Hz, 2H), 4.29– 4.17 (m, 6H). ¹³**C NMR** (101 MHz, CDCl₃) δ = 136.6 (Cq), 136.5 (Cq), 133.3 (CH), 132.4 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.3 (CH), 126.5 (CH), 125.1 (CH), 82.5 (Cq), 82.4 (Cq), 70.2 (CH₂), 66.5 (CH₂), 57.8 (CH₂), 57.4 (CH₂). **(ESI)-HRMS** calcd for C₂₂H₂₂NaO₂ [M + Na]⁺ 341.1512, found 341.1518.

(3a R, 4S, 5S, 8bS)-4,5-Diphenyl-1,3,3a,4,5,6,8,8b- octahydrobenzo[1,2-c:3,4-c']difuran (4a).



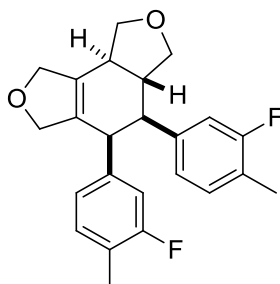
Compound **4a** (166.7 mg, 0.52 mmol, 88% yield, $^1\text{H NMR}$ dr 97:3) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-2** at 45 °C from **3a** (0.6 mmol); $^1\text{H NMR}$ (400 MHz, CD_2Cl_2) δ = 7.16–6.98 (m, 6H), 6.69–6.67 (m, 4H), 4.72–4.71 (m, 2H), 4.45–4.28 (m, 2H), 4.15 (t, J = 6.9 Hz, 1H), 3.80–3.76 (m, 2H), 3.63 (dd, J = 10.8, 7.6 Hz, 1H), 3.41 (dd, J = 11.3, 6.5 Hz, 1H), 3.25 (dd, J = 10.5, 7.8 Hz, 1H), 2.76–2.65 (m, 2H). $^{13}\text{C NMR}$ (101 MHz, CD_2Cl_2) δ = 141.1 (Cq), 138.6 (Cq), 135.5 (Cq), 133.0 (Cq), 130.1 (CH), 128.8 (CH), 128.0 (CH), 127.9 (CH), 126.9 (CH), 126.6 (CH), 76.4 (CH_2), 75.9 (CH_2), 70.1 (CH_2), 70.0 (CH_2), 49.0 (CH), 47.7 (CH), 44.1 (CH), 43.1 (CH). **(ESI)-HRMS** calcd for $\text{C}_{22}\text{H}_{22}\text{KO}_2$ $[\text{M} + \text{K}]^+$ 357.1252, found 357.1253.

(3a R, 4S, 5S, 8bS)-4,5-Di-o-tolyl-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-c:3,4-c']difuran (4b).



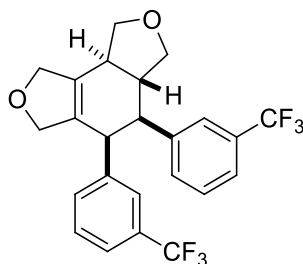
Compound **4b** (43.4 mg, 0.125 mmol, 63% yield, ^{13}C NMR dr 98:2) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-2** at 45 °C from **3b** (0.2 mmol); ^1H NMR (300 MHz, CDCl_3) δ = 7.27 (d, J = 7.2 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 7.07–7.02 (m, 2H), 6.98–6.93 (m, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.63 (t, J = 7.5 Hz, 1H), 5.99 (d, J = 7.8 Hz, 2H), 4.75 (s, 1H), 4.46–4.31 (m, 2H), 4.20 (t, J = 7.0 Hz, 1H), 4.13–4.08 (m, 1H), 3.71–3.63 (m, 3H), 3.19 (dd, J = 11.0, 7.6 Hz, 1H), 2.91–2.67 (m, 2H), 2.46 (s, 3H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ = 138.1 (Cq), 137.8 (Cq), 136.2 (Cq), 136.1 (Cq), 135.6 (Cq), 131.9 (Cq), 130.0 (CH), 129.5 (CH), 128.8 (CH), 127.9 (CH), 126.7 (CH), 126.1 (CH), 125.5 (CH), 125.0 (CH), 76.3 (CH₂), 75.5 (CH₂), 70.1 (CH₂), 69.8 (CH₂), 43.9 (CH), 43.4 (CH), 43.3 (CH), 39.6 (CH), 19.8 (CH₃), 18.5 (CH₃). (ESI)-HRMS calcd for $\text{C}_{24}\text{H}_{26}\text{NaO}_2$ $[\text{M} + \text{Na}]^+$ 369.1830, found 369.1821.

(3aR,4S,5S,8bS)-4,5-Bis(3-fluoro-4-methylphenyl)-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-c:3,4-c']difuran (4c).



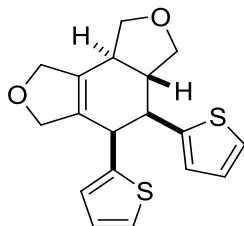
Compound **4c** (24.8 mg, 0.06 mmol, 65% yield, ^1H NMR dr 98:2) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-2** at 45 °C from **3c** (0.1 mmol); ^1H NMR (400 MHz, CDCl_3) δ 6.93–6.89 (m, 2H), 6.39–6.33 (m, 4H), 4.76 (s, 2H), 4.49–4.38 (m, 2H), 4.21 (t, $J = 7.1$ Hz, 1H), 3.85 (t, $J = 7.3$ Hz, 1H), 3.71–3.70 (m, 1H), 3.67 (dd, $J = 11.4, 7.3$ Hz, 1H), 3.36–3.29 (m, 2H), 2.74–2.56 (m, 2H), 2.20 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ = 160.9 (d, $J = 244.3$ Hz, Cq), 139.8 (d, $J_{\text{CF}} = 7.1$ Hz, Cq), 137.4 (d, $J_{\text{CF}} = 6.8$ Hz, Cq), 134.9 (Cq), 132.7 (Cq), 130.8 (d, $J_{\text{CF}} = 5.4$ Hz, CH), 130.6 (d, $J_{\text{CF}} = 5.4$ Hz, CH), 130.1 (Cq), 124.4 (Cq), 123.5 (d, $J_{\text{CF}} = 2.7$ Hz, CH), 123.2 (d, $J_{\text{CF}} = 17.3$ Hz, CH), 122.9 (d, $J_{\text{CF}} = 17.1$ Hz, CH), 115.9 (d, $J_{\text{CF}} = 22.3$ Hz, Cq), 114.7 (d, $J_{\text{CF}} = 22.2$ Hz, CH), 76.1 (CH_2), 75.5 (CH_2), 69.8 (CH_2), 69.7 (CH_2), 48.0 (CH), 46.6 (CH), 43.6 (CH), 42.7 (CH), 14.1 (d, $J_{\text{CF}} = 3.5$ Hz, 2 CH_3). ^{19}F NMR (376 MHz, CDCl_3) δ = 118.2. (ESI)-HRMS calcd for $\text{C}_{24}\text{H}_{24}\text{F}_2\text{NaO}_2$ [$\text{M} + \text{Na}$] $^+$ 405.1642, found 405.1640.

(3aR,4S,5S,8bS)-4,5-Bis(3-(trifluoromethyl)phenyl)-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-c:3,4-c']difuran (4d).



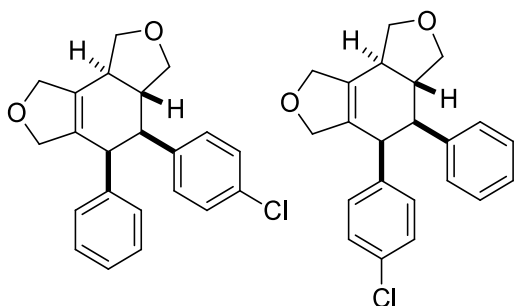
Compound **4d** (55.0 mg, 0.12 mmol, 60% yield, ¹³C NMR dr 89:11) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-2** at 70 °C from **3d** (0.2 mmol); ¹H NMR (400 MHz, acetone-*d*₆) δ = 7.45–7.40 (m, 4H), 7.36–7.32 (m, 2H), 7.23–7.16 (m, 1H), 7.01 (brs, 1H), 4.75 (brs, 2H), 4.47–4.43 (m, 1H), 4.30–4.27 (m, 1H), 4.19–4.13 (m, 2H), 3.79–3.67 (m, 3H), 3.28 (dd, *J* = 10.2, 7.9 Hz, 1H), 2.84–2.72 (m, 2H). ¹³C NMR (101 MHz, acetone-*d*₆) δ = 142.1 (Cq), 139.7 (Cq), 134.2 (Cq), 133.7 (Cq), 132.3 (CH), 129.6 (q, *J*_{CF} = 32.2 Hz, 2 Cq), 128.7 (CH), 128.6 (2CH), 126.6 (br CH), 124.8 (q, *J*_{CF} = 3.6 Hz, CH), 124.3 (q, *J*_{CF} = 271.6 Hz, CF₃), 124.2 (q, *J*_{CF} = 271.7 Hz, CF₃), 123.4 (q, *J*_{CF} = 3.9 Hz, CH), 123.1 (q, *J*_{CF} = 3.9 Hz, CH), 75.4 (CH₂), 75.0 (CH₂), 68.9 (CH₂), 68.9 (CH₂), 47.7 (CH), 46.4 (CH), 43.3 (CH), 42.3 (CH). ¹⁹F NMR (565 MHz, acetone-*d*₆) δ = –63.1. (ESI)-HRMS calcd for C₂₄H₂₀F₆NaO₂⁺ [M + Na]⁺ 477.1260, found 477.1256.

(3aR,4S,5S,8bR)-4,5-Di(thiophen-2-yl)-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-c:3,4-c']difuran (4e).



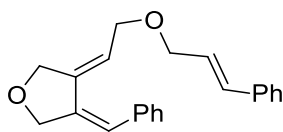
Compound **4e** (72.0 mg, 0.22 mmol, 64% yield, ^1H NMR dr 96:4) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-2** at 45 °C from **3e** (0.34 mmol). ^1H NMR (400 MHz, CDCl_3) δ = 7.10 (dd, J = 5.1, 1.0 Hz, 1H), 7.05 (dd, J = 5.1, 1.2 Hz, 1H), 6.80 (dd, J = 5.1, 3.3 Hz, 1H), 6.79 (dd, J = 5.1, 3.5 Hz, 1H), 6.48 (dt, J = 3.5, 1.2 Hz, 1H), 6.46 (dt, J = 3.3, 1.0 Hz, 1H), 4.69–4.68 (m, 2H), 4.50 (dt, J = 4.76, 3.4, 2H), 4.17 (t, J = 7.1 Hz, 1H), 4.08–4.03 (m, 1H), 4.00 (dd, J = 7.7, 6.8 Hz, 1H), 3.65 (dd, J = 11.6, 1.5 Hz, 1H), 3.63 (dd, J = 11.4, 2.5 Hz, 1H), 3.44 (dd, J = 10.8, 7.7 Hz, 1H), 2.77 (qd, J = 10.8, 6.8 Hz, 1H), 2.72–2.62 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ = 143.2 (C2'), 141.5 (C2''), 135.3 (C6a), 131.9 (C8a), 126.6 (C3''), 126.5, 126.3 (C4'', C4'), 124.9 (C5''), 124.8 (C3'), 123.8 (C5'), 76.3 (C8), 75.5 (C6), 70.2 (C3), 69.7 (C1), 44.1 (C3a), 43.8 (C4), 43.5 (C8b), 43.3 (C5). (ESI)- HRMS calcd for $\text{C}_{18}\text{H}_{18}\text{KO}_2\text{S}_2$ $[\text{M} + \text{K}]^+$ 369.0383, found 369.0382.

**4-(4-Chlorophenyl)-5-phenyl-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-c:3,4-c']difuran
Compound with 5-(4-Chlorophenyl)-4-phenyl-1,3,3a,4,5,6,8,8b-octahydrobenzo- [1,2-c:3,4-c']difuran (4f/4f').**



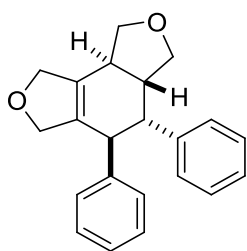
Compounds **4f/4f'** (60.2 mg, 0.17 mmol, 85% yield, $^1\text{H NMR}$ ratio 1.1, $^1\text{H NMR}$ dr 97:3 for both isomers) were obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-2** at 70 °C from **3f** (0.2 mmol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.18–7.05 (m, 12H), 6.69–6.63 (m, 3H), 6.60–6.54 (m, 3H), 4.81–4.64 (m, 4H), 4.50–4.27 (m, 4H), 4.19 (t, J = 7.1 Hz, 2H), 3.90–3.81 (m, 1H), 3.81–3.67 (m, 3H), 3.65 (dd, J = 11.0, 7.1 Hz, 2H), 3.43–3.22 (m, 4H), 2.77–2.54 (m, 4H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 140.0 (Cq), 139.0 (Cq), 137.4 (Cq), 136.4 (Cq), 135.1 (Cq), 134.9 (Cq), 133.0 (Cq), 132.7 (Cq), 132.5 (Cq), 132.2 (Cq), 130.8 (2CH), 129.6 (4CH), 128.2 (2CH), 128.0 (2CH), 127.9 (2CH), 127.9 (2CH), 127.8 (2CH), 127.0 (2CH), 126.7 (2CH), 76.2 (CH_2), 76.1 (CH_2), 75.6 (2 CH_2), 69.9 (CH_2), 69.81 (CH_2), 69.78 (CH_2), 69.7 (CH_2), 48.5 (CH), 48.0 (CH), 47.1 (CH), 46.7 (CH), 43.7 (CH), 43.6 (CH), 42.7 (CH), 42.6 (CH). (ESI)-HRMS calcd for $\text{C}_{22}\text{H}_{21}\text{ClNaO}_2$ $[\text{M} + \text{Na}]^+$ 375.1128, found 375.1135.

(3E,4Z)-3-Benzylidene-4-(2-(cinnamyloxy)ethylidene)- tetrahydrofuran (4g^{III}).



Compound **4g^{III}** (12.1 mg, 0.04 mmol, 19% yield) was obtained as a yellow oil (silica gel, n-hexanes/EtOAc, gradient) following the general procedure **GP-2** at 70 °C from **3g** (0.2 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.43–7.19 (m, 10H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.49 (s, 1H), 6.22 (dt, *J* = 15.9, 6.1 Hz, 1H), 5.93 (dt, *J* = 6.6, 4.0 Hz, 1H), 4.57 (s, 2H), 4.53 (d, *J* = 1.9 Hz, 2H), 4.05 (d, *J* = 6.1 Hz, 2H), 3.92 (d, *J* = 6.5 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 137.5 (Cq), 136.7 (Cq), 136.6 (Cq), 136.6 (Cq), 132.7 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), 127.8 (CH), 127.3 (CH), 126.5 (CH), 125.8 (CH), 121.8 (CH), 120.4 (CH), 74.2 (CH₂), 71.6 (CH₂), 70.8 (CH₂), 67.4 (CH₂). (ESI)-HRMS calcd for C₂₂H₂₂NaO₂ [M + Na]⁺ 341.1517, found 341.1513.

(3a R, 4R, 5S, 8b S)-4,5-Diphenyl-1,3,3a,4,5,6,8,8boctahydrobenzo[1,2-c:3,4-c']difuran (4g).



Compound **4g** (15.5 mg, 0.05 mmol, 24% yield) was obtained as a yellow oil (silica gel, nhexanes/EtOAc, gradient) following the general procedure **GP-2** at 70 °C from **3g** (0.2 mmol); ¹H NMR (400 MHz, CDCl₃) δ = 7.39– 7.21 (m, 8H), 7.08–7.04 (m, 2H), 4.83–4.69 (m, 2H), 4.67–4.55 (m, 2H), 4.03 (t, *J* = 7.2 Hz, 1H), 3.87 (s, 1H), 3.83 (t, *J* = 7.1 Hz, 1H), 3.54 (dd, *J* = 11.2, 7.1 Hz, 1H), 3.22 (d, *J* = 3.8 Hz, 1H), 3.12 (dd, *J* = 11.3, 7.3 Hz, 1H), 2.46 (tdd, *J* = 11.2, 7.0, 3.8 Hz, 1H), 2.37– 2.23 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 143.1 (Cq), 140.7 (Cq), 134.1 (Cq), 133.9 (Cq), 128.9 (2CH), 128.5 (2CH), 128.2 (2CH), 127.9 (2CH), 127.0 (CH), 127.0 (CH), 76.3 (CH₂), 75.8 (CH₂), 68.9 (CH₂), 68.3 (CH₂), 47.6 (CH), 46.2 (CH), 42.7 (CH), 36.0 (CH). (ESI)-HRMS calcd for C₂₂H₂₂NaO₂ [M + Na]⁺ 341.1517, found 341.1526

References

- [1] Kumar, S.; Kumar, V.; Singh, S.P. *Pericyclic reactions, A Mechanistic and Problem-Solving Approach*, **2015**. (a) Funel, J., Abele, S. *Angew. Chem. Int. Ed.* **2013**, 52, 3822 – 3863.
- [2] Nicolau, C. K.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, 41, 1668-1698. 8112.
- [3] Wakayama, H.; Sakai, S. *J. Phys. Chem. A* **2007**, 111, 13575.
- [4] Wessing, P.; Müller, G.; *Chem. Rev.* **2008**, 108, 2051–2063
- [5] (a) Michael, A.; Bucher, J. E. *Chem. Ber.* **1895**, 28, 2511. (b) Michael, A.; Bucher, J. E. *Am. Chem. J.* **1898**, 20, 89. (c) Bucher, J. E. *J. Am. Chem. Soc.* **1908**, 30, 1244 (d) Pfeiffer, P.; Müller, W. *Chem. Ber.* **1907**, 40, 384
- [6] Baddar, F. G.; Moussa, G. E. M.; Omar, M. T. *J. Chem. Soc.* **1968**, 110.
- [7] (a) Klemm, L. H.; Gopinath, K. W.; Hsu Lee, D.; Kelly, F. W.; Trod, E.; McGuire, T. M. *Tetrahedron* **1966**, 22, 1797. (b) Klemm, L. H.; Hsu Lee, D.; Gopinath, K. W.; Klopfenstein, C. E. *J. Org. Chem.* **1966**, 31, 2376. (c) Klemm, L. H.; Klemm, R. A.; Santhanam, P. S.; White, D. V. *J. Org. Chem.* **1971**, 36, 2169. (d) Klemm, L. H.; McGuire, T. M.; Gopinath, K. W. *J. Org. Chem.* **1976**, 41, 2571. (e) Anastas, P. T.; Stevenson, R. *J. Nat. Prod.* **1991**, 54, 1687. (f) Stevenson, R.; Weber, J. *J. Nat. Prod.* **1989**, 52, 367
- [8] Rodriguez, D.; Vasquez, A., Castedo, L., Dominguez D.; Saa', C. *J. Am. Chem. Soc.* **2001**, 123, 9178-9179
- [9] Wessig, P.; Matthes, A.; Pick, C., *Org. Biomol. Chem.*, **2011**, 9, 7599-7605
- [10] P. Wessig, G. Muller, C. Pick and A. Matthes, *Synthesis*, **2007**, 464.
- [11] P. Wessig, G. Muller, A. Kuhn, R. Herre, H. Blumenthal and S. Troelenberg, *Synthesis*, **2005**, 1445
- [12] P. Wessig, G. Muller, R. Herre and A. Kuhn, *Helv. Chim. Acta*, **2006**, 89, 2694.
- [13] P. Wessig and G. Muller, *Chem. Commun.*, **2006**, 4524
- [14] Klemm, L. H.; Gopinath, K. W. *Tetrahedron Lett.* **1963**, 4, 1243.
- [15] Chackalamannil, S., Doller, D., Eagen, K. *Tetrahedron Lett.* **2002**, 43, 5101–5103
- [16] Ozawa, T., Kurahashi, T., Matsubara, S. *Org. Lett.* **2011**, 13, 5390-5393
- [17] Kocsis, L. S., Kagalwala, H., N., Mutto, S., Godugu, B., Bernhard, S., Tantillo, D., J., Brummond, K., M. J. *Org. Chem.* **2015**, 80, 11686–11698
- [18] Mun, H. J.; Seong, E. Y.; Ahn, K. H.; Kang, E. J. *J. Org. Chem.* **2018**, 83, 1196 -1203.
- [19] Chen, X.; Zhong, C.; Lu, Y.; Yao, M.; Guan, Z.; Chen, C.; Zhu, H.; Luo, Z.; Zhang, Y. *Chem. Commun.* **2021**, 57, 5155.

- [20] (a) Houk, K. N.; Liu, F.; Yang, Z.; Seeman, J. I. *Evolution of the Diels–Alder Reaction Mechanism since the 1930s: Woodward, Houk with Woodward, and the Influence of Computational Chemistry on Understanding Cycloadditions*. *Angew. Chem., Int. Ed.* **2021**, 60, 12660. (b) Lording, W. J.; Fallon, T.; Sherburn, M. S.; Paddon-Row, M. N. *The simplest Diels–Alder reactions are not endo-selective*. *Chem. Sci.* **2020**, 11, 11915. (c) Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Hoi Hong Li, W.; Daoust, K. J.; Boddington Bovee, L.; Di Rico, K. J.; Johnson, R. P. *Concerted vs Stepwise Mechanisms in Dehydro-Diels–Alder Reactions*. *J. Org. Chem.* **2011**, 76, 9320. (d) Beno, B. R.; Houk, K. N.; Singleton, D. A. *Synchronous or Asynchronous? An “Experimental” Transition State from a Direct Comparison of Experimental and Theoretical Kinetic Isotope Effects for a Diels–Alder Reaction*. *J. Am. Chem. Soc.* **1996**, 118, 9984.
- [21] (a) Fluegel, L. L.; Hoyer, T. R. *Hexadehydro-Diels–Alder Reaction: Benzyne Generation via Cycloisomerization of Tethered Triynes*. *Chem. Rev.* **2021**, 121, 2413. (b) Desimoni, G.; Faita, G.; Quadrelli, P. *Forty Years after “Heterodiene Syntheses with α,β -Unsaturated Carbonyl Compounds”: Enantioselective Syntheses of 3,4-Dihydropyran Derivatives*. *Chem. Rev.* **2018**, 118, 2080. (c) Oliveira, B. L.; Guo, Z.; Bernardes, G. J. L. *Inverse electron demand Diels–Alder reactions in chemical biology*. *Chem. Soc. Rev.* **2017**, 46, 4895. (d) Klas, K.; Tsukamoto, S.; Sherman, D. H.; Williams, R. M. *Natural Diels–Alderase: Elusive and Irresistible*. *J. Org. Chem.* **2015**, 80, 11672.
- [22] (a) Brummond, K. M.; Kocsis, L. S. *Intramolecular DidehydroDiels–Alder Reaction and Its Impact on the Structure–Function Properties of Environmentally Sensitive Fluorophores*. *Acc. Chem. Res.* **2015**, 48, 2320. (b) Benedetti, E.; Kocsis, L. S.; Brummond, K. M. *Synthesis and Photophysical Properties of a Series of Cyclopenta[b]naphthalene Solvatochromic Fluorophores*. *J. Am. Chem. Soc.* **2012**, 134, 12418.
- [23] Gaussian 09, Revision A.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**.
- [24] Zhao, Y.; Truhlar, D. G. *Theor. Chem. Account* **2008**, 120, 215.
- [25] (a) Weigen, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, 7, 3297; (b) Andrae, D.; Haeussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Theor. Chim. Acta* **1990**, 77, 123; (c) Peterson, K. A.; Figgen, D.; Goll, E.; Stoll, H.; Dolg, M. *J. Chem. Phys.* **2003**, 119, 11113.

- [26] (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, 102, 1995; (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, 24, 669; (c) Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans* **1993**, 2, 799; (d) Schäfer, A.; Klamt, A.; Sattel, D.; Lohrenz, J. C. W.; Eckert, F. *Phys. Chem. Chem. Phys.* **2000**, 2, 2187.
- [27] Besora, M.; Braga, A. A. C.; Ujaque, G.; Maseras, F.; Lledós, A. *Theor. Chem. Acc.* **2011**, 128, 639.
- [28] Benedetti, E.; Simonneau, A.; Hours, A.; Amouri, H.; Penoni, A.; Palmisano, G.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. *Adv. Synth. Catal.* **2011**, 353, 1908. S156.
- [29] Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem. Int. Ed.* **2008**, 47, 4729.
- [30] Malkov, A. V.; Gouriou, L.; Lloyd-Jones, G. C.; Stary, I.; Langer, V.; Spoor, P.; Vinader, V.; Kocovsky, P. *Chem. Eur. J.* **2006**, 12, 6910.
- [31] M. Lanzi, T. Cañeque, L. Marchiò, R. Maggi, F. Bigi, M. Malacria and G. Maestri, *ACS Catal.*, **2018**, 8, 144.
- [32] C. Cecchini, G. Cera, M. Lanzi, L. Marchio; M. Malacria and G. Maestri, *Org. Chem. Front.*, **2019**, 6, 3584
- [33] L. L. Fluegel and T. R. Hoye, *Chem. Rev.*, **2021**, 121, 2413.
- [34] W. Li, L. Zhou and J. Zhang, *Chem. Eur. J.*, **2016**, 22, 1158
- [35] N. Camedda, M. Lanzi, F. Bigi, R. Maggi and G. Maestri, *Org. Lett.*, **2021**, 23, 6536.
- [36] Liu, R.; Chou, Y.; Lian, B.; Fang, D.; Gao, M.; Cheng, Liu, G. *Org. Lett.* **2019**, 21, 6815–6820
- [37] Liu, R.; Ni, Z.; Giordano, L.; Tenaglia, A. *Org. Lett.* **2016**, 18, 4040–4043
- [38] Smedley, C.J.; Barrow, A.S.; Spiteri, C.; Giel, M.C.; Sharma, P.; Moses, J.E. *Chem. Eur. J.* **2017**, 23, 9990–9995.
- [39] Jette, C. I.; Tong, Z. J.; Hadt, R. G.; Stoltz, B. *Angew. Chem. Int. Ed.* **2020**, 59, 2033–2038.
- [40] (a) Sattler, A. *ACS Catal.* **2018**, 8, 2296. (b) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. *Angew. Chem. Int. Ed.* **2018**, 57, 3022. (c) Navratil, A. R.; Shchepinov, M. S.; Dennis, E. A. *J. Am. Chem. Soc.* **2018**, 140, 235. (d) Gant, T. G. *J. Med. Chem.* **2014**, 57, 3595. (e) Katsnelson, A. *Nat. Med.* **2013**, 19, 656. (f) Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, 51, 3066. (g) Isin, E. M.; Elmore, C. S.; Nilsson, G. N.; Thompson, R. A.; Weidolf, L. *Chem. Res. Toxicol.* **2012**, 25, 532. (h) Elmore, C. S. *Annu. Rep. Med. Chem.* **2009**, 44, 515.
- [41] (a) Zarate, C.; Yang, H.; Bezdek, M. J.; Hesk, D.; Chirik, P. J. *J. Am. Chem. Soc.* **2019**, 141, 5034. (b) Kerr, W. J.; Lindsay, D. M.; Owens, P. K.; Reid, M.; Tuttle, T.; Campos, S. *ACS Catal.* **2017**, 7, 7182. (c) Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2014**, 53, 734. (d) Emmert, M. H.; Gary, B. J.; Villalobos, J. M.; Sanford, M. *Angew. Chem. Int. Ed.* **2010**, 49, 5884. (e) Martins, A.; Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, 12, 5186. (f) Precht, M. H. G.; Holscher, M.; Ben-David, Y.; Theyssen, N.; Loschen, R.; Milstein, D.; Leitner, W. *Angew. Chem. Int. Ed.* **2007**, 46, 2269.

- [42] (a) Muller, V.; Weck, R.; Derdau, V.; Ackermann, L. *Chem. CatChem* **2020**, 12, 100. (b) Valero, M.; Becker, D.; Jess, K.; Weck, R.; Atzrodt, J.; Bannenberg, T.; Derdau, V.; Tamm, M. *Chem. Eur. J.* **2019**, 25, 6517. (c) Valero, M.; Weck, R.; Gussregen, S.; Atzrodt, J.; Derdau, V. *Angew. Chem. Int. Ed.* **2018**, 57, 8159. (d) Kaphan, D. M.; Klet, R. C.; Perras, F. A.; Pruski, M.; Yang, C.; Kropf, J.; Delferro, M. *ACS Catal.* **2018**, 8, 5363. (e) Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; MacMillan, D. W. C. *Science* **2017**, 358, 1182. (f) Pony, Yu. R.; Hesk, D.; Rivera, N.; Pelczar, I.; Chirik, P. J. *Nature* **2016**, 529, 195.
- [43] (a) Trost, B. M.; Tracy, J. S. *ACS Catal.* **2019**, 9, 1584. (b) Wang, J.; Dong, Z.; Yang, C.; Dong, G. *Nat. Chem.* **2019**, 11, 1106. (c) Maestri, G.; Derat, E. *Nat. Chem.* **2019**, 11, 1082.
- [44] (a) Puleo, T. R.; Strong, A. J.; Bandar, J. S. *J. Am. Chem. Soc.* **2019**, 141, 1467. (b) Di Giuseppe, A.; Castarlenas, R.; Pérez-Torrente, J. J.; Lahoz, F. J.; Oro, L. A. *Chem. Eur. J.* **2014**, 20, 8391. (c) Hatano, M.; Nishimura, T.; Yorimitsu, H. *Org. Lett.* **2016**, 18, 3674.
- [45] (a) Cera, G.; Della Ca', N.; Maestri, G. *Chem. Sci.* **2019**, 10, 10297. (b) Cecchini, C.; Lanzi, M.; Cera, G.; Malacria, M.; Maestri, G. *Synthesis* **2019**, 51, 1216. (c) Lanzi, M.; Cañeque, T.; Marchio, L.; Maggi, R.; Bigi, F.; Malacria, M.; Maestri, G. *ACS Catal.* **2018**, 8, 144. (d) Cera, G.; Lanzi, M.; Balestri, D.; Della Ca', N.; Maggi, R.; Bigi, F.; Malacria, M.; Maestri, G. *Org. Lett.* **2018**, 20, 3220. (e) Cera, G.; Lanzi, M.; Bigi, F.; Maggi, R.; Malacria, M.; Maestri, G. *Chem. Commun.* **2018**, 54, 14021. (f) Monfredini, A.; Santacroce, V.; Marchio, L.; Maggi, R.; Bigi, F.; Maestri, G.; Malacria, M. *ACS Sustainable Chem. Eng.* **2017**, 5, 8205
- [46] (a) Zheng, P.; Wang, C.; Chen, Y.-C.; Dong, G. *ACS Catal.* **2019**, 9, 5515. (b) Haydl, A. M.; Breit, B.; Lang, T.; Krische, M. J. *Angew. Chem. Int. Ed.* **2017**, 56, 11312. (c) McCammant, M.; Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, 135, 4167. (d) Lichtenberg, C.; Okuda, J. *Angew. Chem. Int. Ed.* **2013**, 52, 5228. (e) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, 47, 258. (f) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 103, 2921. For selected examples involving allylic alcohols, see: (g) Liu, Q.; Wu, L.; Jiao, H.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* **2013**, 52, 8064. (h) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *Adv. Synth. Catal.* **2006**, 348, 1101. (i) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H.; Yoshifuji, M. *Organometallics* **2004**, 23, 1698. (j) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Mol. Catal. A: Chem.* **1996**, 111, 43.
- [47] (a) Lu, Z.; Yoon, T. P. *Angew. Chem. Int. Ed.* **2012**, 51, 10329. (b) Poplata, S.; Troster, A.; Zou, Y.-Q.; Bach, T. *Chem. Rev.* **2016**, 116, 9748
- [48] Martín, N.; Scott, L. T. *Challenges in Aromaticity: 150 Years after Kekule's Benzene*. *Chem. Soc. Rev.* **2015**, 44, 6397.
- [49] Frogley, B. J.; Wright, L. J. *Recent Advances in Metallaaromatic Chemistry*. *Chem. - Eur. J.* **2018**, 24, 2025.
- [50] Blanchard, S.; Fensterbank, L.; Gontard, G.; Lacôte, E.; Maestri, G.; Malacria, M. *Synthesis of Triangular Tripalladium Cations as Noble-Metal Analogues of the Cyclopropenyl Cation*. *Angew. Chem., Int. Ed.* **2014**, 53, 1987.

- [51] Wang, Y.; Monfredini, A.; Deyris, P.-A.; Blanchard, F.; Derat, E.; Maestri, G.; Malacria, M. *All-Metal Aromatic Cationic Palladium Triangles Can Mimic Aromatic Donor Ligands with Lewis Acidic Cations*. *Chem. Sci.* **2017**, 8, 7394.
- [52] Kulichenko, M.; Fedik, N.; Monfredini, A.; Munoz-Castro, A.; Balestri, D.; Boldyrev, A. I.; Maestri, G. “Bottled” spiro-doubly aromatic trinuclear $[Pd_2Ru]^+$ complexes. *Chem. Sci.* **2021**, 12, 477.
- [53] Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Cycloisomerization of 1,n-Enynes: Challenging Metal-Catalyzed Rearrangements and Mechanistic Insights*. *Angew. Chem., Int. Ed.* **2008**, 47, 4268.
- [54] Aubert, C.; Buisine, O.; Malacria, M. *The Behavior of 1, n -Enynes in the Presence of Transition Metals*. *Chem. Rev.* **2002**, 102, 813.
- [55] Hu, Y.; Bai, M.; Yang, Y.; Zhou, Q. *Metal-Catalyzed Enyne Cycloisomerization in Natural Product Total Synthesis*. *Org. Chem. Front.* **2017**, 4, 2256.
- [56] Stathakis, C. I.; Gkizis, P. L.; Zografos, A. L. *Metal-Catalyzed Cycloisomerization as a Powerful Tool in the Synthesis of Complex Sesquiterpenoids*. *Nat. Prod. Rep.* **2016**, 33, 1093.
- [57] Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J.; Thomas, A. P. *The Palladium-Catalyzed Enyne Cycloisomerization Reaction in a General Approach to the Asymmetric Syntheses of the PicROTOXANE Sesquiterpenes. Part I. First-Generation Total Synthesis of Corianin and Formal Syntheses of PicROTOXININ and PicROTIIN*. *J. Am. Chem. Soc.* **1999**, 121, 6183.
- [58] Düfert, A.; Werz, D. B. *Carbopalladation Cascades Using Carbon-Carbon Triple Bonds: Recent Advances to Access Complex Scaffolds*. *Chem. - Eur. J.* **2016**, 22, 16718.
- [59] Fürstner, A.; Stelzer, F.; Szillat, H. *Platinum-Catalyzed Cycloisomerization Reactions of Enynes*. *J. Am. Chem. Soc.* **2001**, 123, 11863.
- [60] Jiménez-Núñez, E.; Echavarren, A. M. *Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective*. *Chem. Rev.* **2008**, 108, 3326.
- [61] Fu, F.; Xiang, J.; Cheng, H.; Cheng, L.; Chong, H.; Wang, S.; Li, P.; Wei, S.; Zhu, M.; Li, Y. *A Robust and Efficient Pd_3 Cluster Catalyst for the Suzuki Reaction and Its Odd Mechanism*. *ACS Catal.* **2017**, 7, 1860.
- [62] Diehl, C. J.; Scattolin, T.; Englert, U.; Schoenebeck, F. *C–I Selective Cross-Coupling Enabled by a Cationic Palladium Trimer*. *Angew. Chem., Int. Ed.* **2019**, 58, 211
- [63] Lanzi, M.; Cañeque, T.; Marchio, L.; Maggi, R.; Bigi, F.; Malacria, M.; Maestri, G. *Alternative Routes to Tricyclic Cyclohexenes with Trinuclear Palladium Complexes*. *ACS Catal.* **2018**, 8, 144
- [64] Cecchini, C.; Lanzi, M.; Cera, G.; Malacria, M.; Maestri, G. *Complementary Reactivity of 1,6-Enynes with All-Metal Aromatic Trinuclear Complexes and Carboxylic Acids*. *Synthesis* **2019**, 51, 1216

- [65] Serafino, A.; Balestri, D.; Marchio, L.; Malacria, M.; Derat, E.; Maestri, G. *Orthogonal Syntheses of 3.2.0 Bicycles from Enallenes Promoted by Visible Light*. *Org. Lett.* **2020**, 22, 6354.
- [66] Lanzi, M.; Santacroce, V.; Balestri, D.; Marchio, L.; Bigi, F.; Maggi, R.; Malacria, M.; Maestri, G. *Visible-Light Promoted Polycyclizations of Dienynes*. *Angew. Chem., Int. Ed.* **2019**, 58, 6703.
- [67] Ren, S. C.; Zhang, F. L.; Qi, J.; Huang, Y. S.; Xu, A. Q.; Yan, H. Y.; Wang, Y. F. *Radical Borylation/Cyclization Cascade of 1,6-Enynes for the Synthesis of Boron-Handled Hetero- and Carbocycles*. *J. Am. Chem. Soc.* **2017**, 139, 6050.
- [68] Zhang, T.; Fu, L.; Gutekunst, W. R. *Practical Synthesis of Functional Metathesis Initiators Using Enynes*. *Macromolecules* **2018**, 51, 6497.
- [69] Dieckmann, M.; Jang, Y. S.; Cramer, N. *Chiral Cyclopentadienyl Iridium(III) Complexes Promote Enantioselective Cycloisomerizations Giving Fused Cyclopropanes*. *Angew. Chem., Int. Ed.* **2015**, 54, 12149.
- [70] Pal, S.; Lucarini, F.; Ruggi, A.; Kilbinger, A. F. M. *Functional Metathesis Catalyst Through Ring Closing Enyne Metathesis: One Pot Protocol for Living Heterotelechelic Polymers*. *J. Am. Chem. Soc.* **2018**, 140, 3181.
- [71] Hayashi, N.; Hirokawa, Y.; Shibata, I.; Yasuda, M.; Baba, A. *Hydroindation of Allenes and Its Application to Radical Cyclization*. *Org. Biomol. Chem.* **2008**, 6, 1949.
- [72] Scholz, S. O.; Kidd, J. B.; Capaldo, L.; Flikweert, N. E.; Littlefield, R. M.; Yoon, T. P. *Construction of Complex Cyclobutane Building Blocks by Photosensitized [2 + 2] Cycloaddition of Vinyl Boronate Esters*. *Org. Lett.* **2021**, 23, 3496.
- [73] Ramana, C. V.; Induvadana, B. A formal synthesis of (+)-didemniserinolipid B employing a Pd-mediated 6-endo selective alkynediol cycloisomerization. *Tetrahedron Lett.* **2009**, 50, 271.
- [74] Miller, R.; Carreras, J.; Muratore, M. E.; Gaydou, M.; Camponovo, F.; Echavarren, A. M. *Broad Scope Aminocyclization of Enynes with Cationic JohnPhos–Gold(I) Complex as the Catalyst*. *J. Org. Chem.* **2016**, 81, 1839.
- [75] Xu, H.-L.; Popov, I. A.; Tkachenko, N. V.; Wang, Z.-C.; MunozCastro, A.; Boldyrev, A. I.; Sun, Z.-M. *σ -Aromaticity-Induced Stabilization of Heterometallic Supertetrahedral Clusters [Zn₆Ge₁₆]⁴⁻ and [Cd₆Ge₁₆]⁴⁻*. *Angew. Chem., Int. Ed.* **2020**, 59, 17286.
- [76] Wang, Z.-C.; Tkachenko, N. V.; Qiao, L.; Matito, E.; MunozCastro, A.; Boldyrev, A. I.; Sun, Z.-M. *All-metal σ -antiaromaticity in dimeric cluster anion {[CuGe₉Mes]₂}⁴⁻*. *Chem. Commun.* **2020**, 56, 6583.
- [77] Liu, C.; Popov, I. A.; Chen, Z.; Boldyrev, A. I.; Sun, Z.-M. *Aromaticity and Antiaromaticity in Zintl Clusters*. *Chem. - Eur. J.* **2018**, 24, 14583.

- [78] Harvey, R.; Mackay, E. G.; Roger, L.; Paddon-Row, M. N.; Sherburn, M.; Lawrence, A. L. *Total Synthesis of Ramonanins A-D. Angew. Chem., Int. Ed.* **2015**, 54, 1795
- [79]. Bigi, F., Cera, G., Maggi, R., Wang, Y., Malacria, M., Maestri, G. *Phys. Chem. A* **2021**, 125, 46, 10035–10043