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UNIVERSITA' DEGLI STUDI DI PARMA

DOTTORATO DI RICERCA IN
Scienze Chimiche

CICLO XXXI

Molecular complexity *via* domino reactions

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1. Overview

Catalysis represents one of the most investigated aspect in chemistry. Nowadays, 85 % to 90 % of all commercial chemicals is produced by methods that involve at least one catalysed step. The economic importance is immediately evident from the estimate world market, assigned about 10 billion US$. The products of these processes, however, were valued at 200 – 300 times that of catalysts. These products could find out broad applications and market, starting from petrol derivatives, building blocks and fine chemicals. Nevertheless, nature is the first catalyst perfectionist, using widespread types of enzymes to support life. Catalysis, thus, is indispensable and ubiquitous.

This thesis deals with complementary aspects of catalysis, namely the use of palladium complexes to trigger domino sequences through alkyne activation and the use of photocatalysts to exploit visible light in organic synthesis.

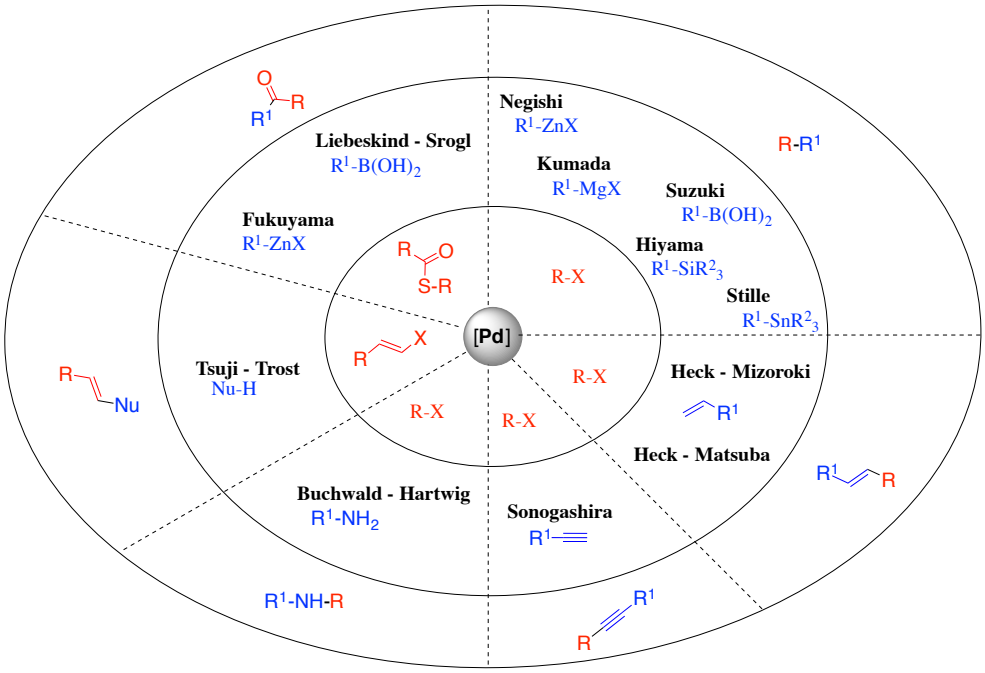
2. Introduction to palladium catalysis

Until the 1970s, the three metals that have been most useful in coupling chemistry were copper, nickel, and palladium, which appeared to show unique strengths. Copper dominated the landscape of acetylene chemistry, nickel had proven a robust solution to the problems of Grignard coupling selectivity, and palladium seemed to be "jack of all trades" offering improved selectivity over the other two metals of the triumvirate. These considerations were based on the excellent activity of palladium catalysts. Indeed, the application of palladium is characterized by singular features and synthetic vantage. Mild reaction conditions minimize the formation of unwanted side products and consequentially provide high selectivity. The use of aryl and heteroaryl halides as reagents, instead of alkalimetal reagents that are extremely sensitive to reaction settings, leads to handy protocols. The wholesale tolerance of both coupling partners offers to palladium catalysed methodologies high chemoselectivity. Furthermore, the high stability of organopalladium compounds to water and air enables easy processing and lower costs. These methods can be robust and scalable. At the end, cross coupling reactions allow for shorter and more selective reaction sequences to the desired products compared to non-catalytic routes. Thanks to the excellent properties of palladium catalysis, cross-coupling methods represent an important answer to many synthetic organic chemistry issues. Nevertheless, they present weak points as well, such as the cost of precious metal and ligands, the production of at least one equivalent of waste salt per mole of product and potential contamination of metal residues in final products. [1]

2.1 Palladium cross-coupling – carbon-carbon bond formation

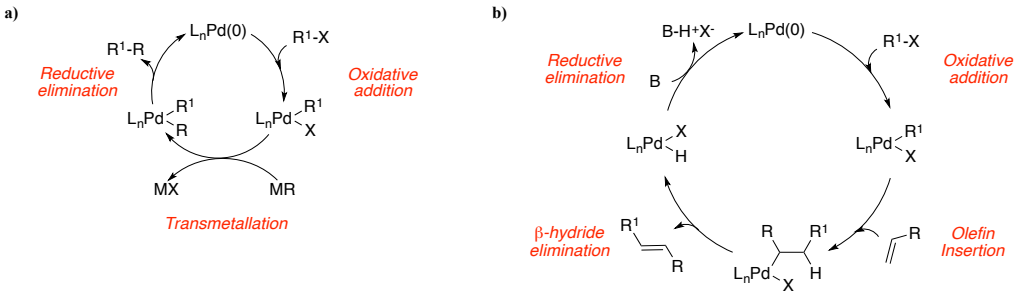
Inspired by the previously metal mediated C-C bond formation reactions, in 1970s, Heck[2] and Mizoroki[3] reported independently a reaction that involved an olefin and an aryl-halide. This signed the beginning of palladium coupling decades. As mentioned before, acetylene chemistry was mostly associated to copper catalysis. In 1975 Sonogashira report the use of catalytic copper instead of a stoichiometric organocuprate reagent. [4] Up to this point, the hybridization of the carbon partner was confined to C-sp^2 and C-sp ones. However, between 1975 and 1979 the activity of palladium catalysis was deeply explored.

In 1977, during his studies on nickel catalysis, Negishi introduced a coupling reaction that used an unsaturated organozinc reagent under mild conditions with impressive group-compatibility. [5] Thus, the concept of cross-coupling was extended to less electropositive-metal species.



Scheme 1 Pd-catalyzed cross-coupling reactions. R = organic group; X = halogen atom or equivalent; Nu = nucleophile such as enolate or amine; [Pd] = Palladium catalyst.

A further study was dedicated to organosilanes reagents but these were not observed to undergo coupling reactions. In the 1980s, on the previous survey of Eaborn and Migita, Stille and Milstein reported the synthesis of ketones. [6] This palladium coupling occurs between an aryl chloride and an organostannane reagent under mild conditions. Despite the number of patents and publications, this reaction suffers from the use of toxic reagents. Suzuki and Miyaura [7], in 1979, described the catalytic cross-coupling within 1-alkenylboranes and arylhalides, expanding the stoichiometric reaction reported by Heck in 1975. [8] Due to the extremely powerful and general method to form a new C-C bond, Suzuki-Miyamura reaction find vast application in industry. A further innovative and clean cross-coupling was reported by Hiyama in 1988, in which he described a cross-coupling within an organosilane and an aryl halides. [9] A fluorine source showed to be required to activate the organosilane in the transmetallation step. The Hiyama coupling provided a complementary and safe option compared to the organoboron, organozinc, and organostannane reagents. These palladium cross-couplings shown in 1979 the possibility to replace nickel catalysed ones. Indeed, Muhasashi reported the first organomagnesium palladium-catalysed cross-coupling. [10] That result came from the previous works of Corriu-Kumada nickel cross-coupling reported in early 1972. [11]

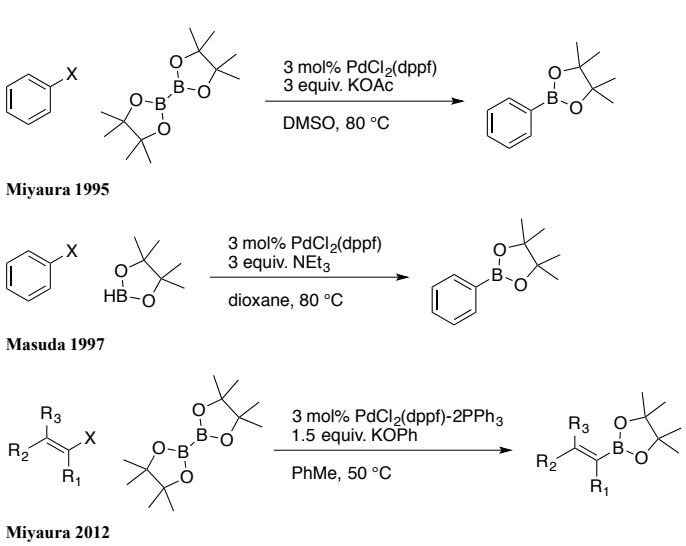


Scheme 2 a) Standard mechanism for Pd cross-coupling; **b)** Standard mechanism for Pd cross-coupling Heck reactions

The mechanism of palladium cross-coupling can be simplified in three substeps, namely the oxidative addition, the transmetallation and the reductive elimination. In Heck reaction, which involves an olefin as reagent, the transmetallation is replace by *syn*-insertion and β-elimination.

2.2 Palladium cross-coupling – carbon-heteroatom bond formation

Up to this point in the cross-coupling reactions, carbon-carbon bonds only were formed, but from the 1990s these reactions were extended to heteroatoms. [12] On the base of Miyaura and Suzuki previous studies, they reported the addition of $B_2(pin)_2$ ($B_2(pin)_2$ = bis(pinacolato)diboron) across a triple bond under [$Pt(PPh_3)_4$] catalysis. [13] This showed that boron could be a partner in cross-coupling reactions. Miyaura in 1995 reported the first palladium catalysed cross-coupling within aryl halides and $B_2(pin)_2$ as partner in presence of KOAc as a base, leading to an aryl borane. [14,15] Despite a low atom economy, introducing an efficient and easy alternative synthetic strategy to prepare aryl boranes useful for Suzuki reactions was really a breakthrough. A further reduction of waste was reported by Masuda in 1997, using HB(pin) and

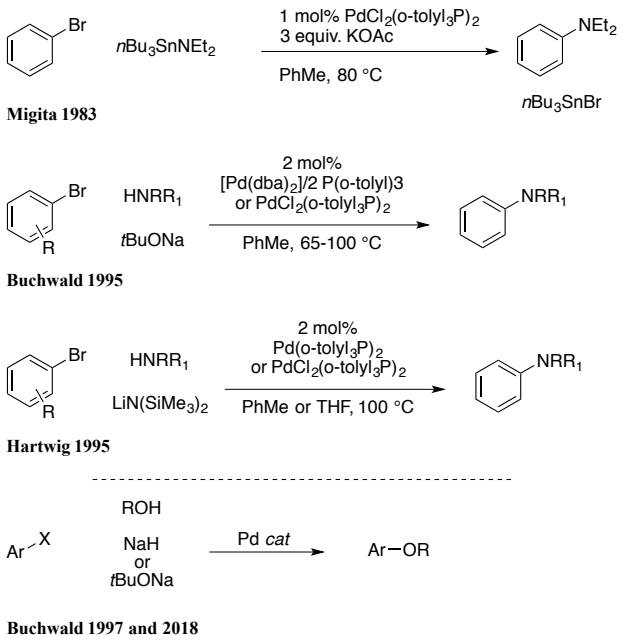


Scheme 3 Examples of carbon-boron cross-coupling

TEA (HB(pin) = pinacolorane; TEA = triethylamine). [16]

The evolution of carbon-heteroatoms bond formation *via* cross-coupling moved on to nitrogen atoms. Migita in 1983 discover the first palladium-catalysed carbon-nitrogen bond formation, involving tributyltin amine salts and aryl halides. [17] This methodology suffered from the high toxicity, cost and high sensibility of the tin reagent to moisture and temperature, therefore the study of C-N coupling was further investigated to employ bare amines. An little-known paper, published by Yagupol'skii in 1986, followed these idea. He reported the first direct carbon amination catalysed by palladium using the sodium salt of an amine derivates. [18] In 1995, Buchwald and Hartwig, independently reported the direct amination employing strong bases such as NaO*t*Bu and LiHMDS (HMDS = 1,1,1,3,3,3- hexamethyldisilazane), respectively. [19,20]

The consecutive studies of Buchwald on carbon-heteroatom bonds shifted to carbon-oxygen ones. In 1997, he reported the first intermolecular palladium catalysed C-O coupling to obtain phenol ethers from alcohols and aryl halides. [21] His studies are currently ongoing and recently he reported a methodology that involves primary alcohols. [22]



Scheme 4 Examples of carbon-nitrogen, carbon-oxygen cross-coupling

Due to the relevance in biology and pharmacy, important attentions were turned to carbon-sulphur cross-couplings. Already in 1978, Migita described the

first carbon-sulphur coupling using aryl halides and thioethers. Later, this methodology was applied to biologically active molecules. [23] The importance phosphines as a ligands and the pharmaceutical interest into carbon-phosphorus bond have received particular attentions. Because of these important applications, many studies were reported to trigger C-P forming cross-couplings. [24] Further important carbon-heteroatom cross-couplings involve formation of C-Se and C-Te bonds. [25]

2.3 Ligands rules in palladium catalysis

During the discovery of palladium cross-coupling reactions, researchers started to map the effects of ligands on the steps of the catalytic cycle (oxidative addition, transmetalation, and reductive elimination). The first evidence was reported by Kumada in 1979 employing bidentate ligands instead of triphenylphosphine. [26] In the following years the effects of ligands were recognized also in other cross-coupling reactions. Starting from that, many types of ligands were introduced and the impact of their choice was rationalized by the introduction of the "*cone angle*" by Tolman, followed by the concept of "*bite angle*". [27,28] Nowadays, the effect of phosphines is often predictable. The use of electron donating ligands, such as trialkyl phosphines, increases the electron density around the metal accelerating the oxidative addition. Sterically hindered ligands, with high value of Tolmann angle, improve the rate of reductive elimination. Phosphine ligands have been replaced by N-heterocyclic carbenes (NHCs). They present some advantages over phosphines, including higher stability toward oxidation and stronger σ-donation that permit to access oxidative addition of aryl chloride. Likewise, NHCs easy customization could lead to highly bulky structures, to promote complex reductive eliminations or further modification of electronic

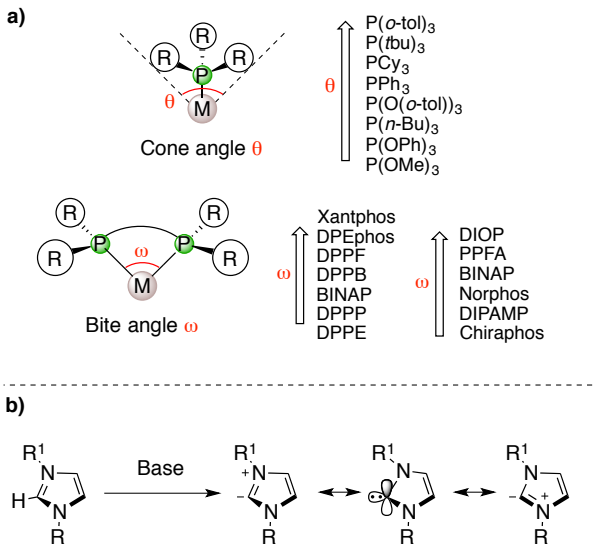


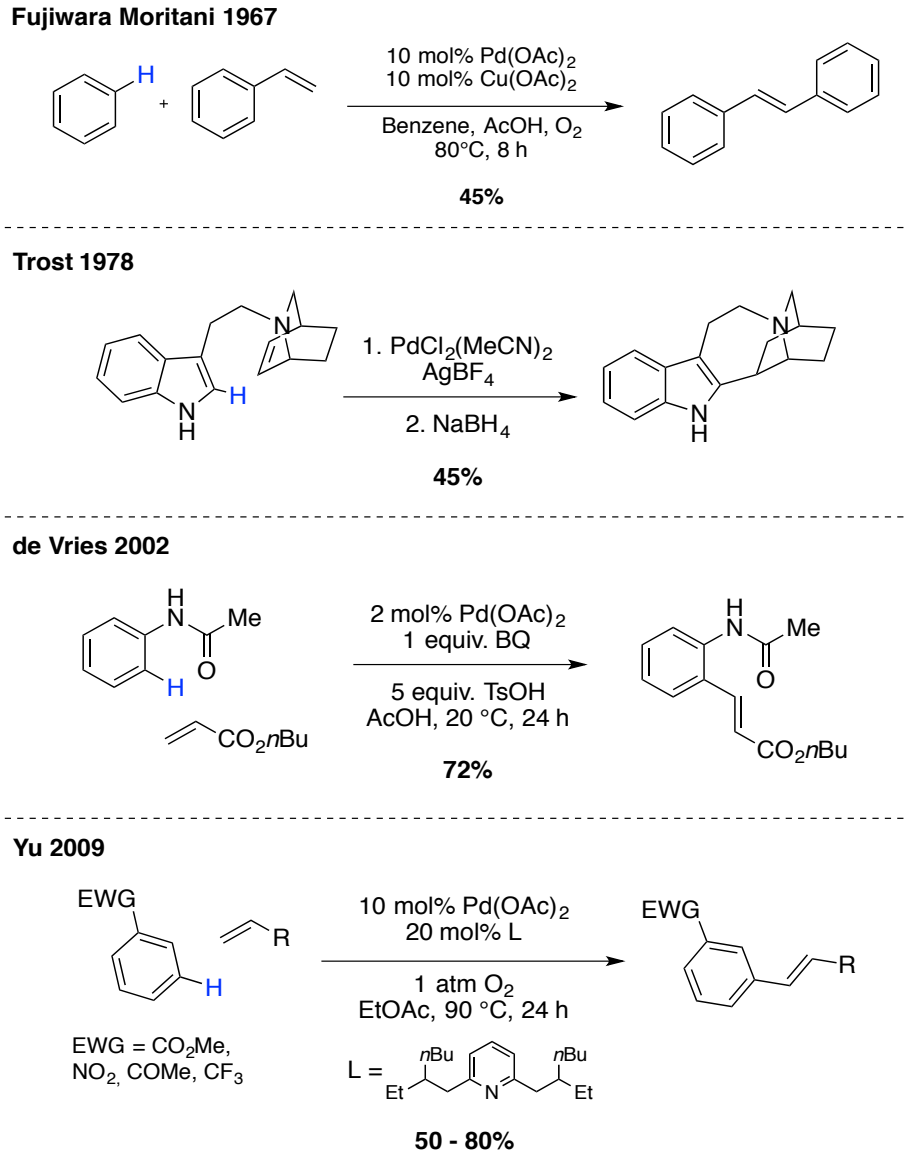
Figure 1 a) Cone angle and Bite angles of commons phosphines; **b)** Preparation and electronic stabilization of anion

properties. [29] Several optically active phosphines and NHCs, axially chiral and P-chiral centers have been developed and applied to catalytic asymmetric reaction.

2.4 Palladium C-H activation

One of the main topic in transition metal catalysis nowadays is the C-H activation. Organic chemists are attracted to discover an alternative route to classic cross-coupling reactions to avoid the use of aryl halides or pseudo halides and organometallic reagents, in order to achieve higher atom economy. A report from Fujiwara in 1969, whom reported the oxidative Heck reaction two years before the Heck and Mizoroki publications, could be considered the first example of C-H activation. [30]

Unfortunately, this methodology present two drawbacks, the use of arenes as solvent and a low control of regioselectivity. Another example was reported by Itahara in 1983 in olefination of indoles, in which an unselective alkylation in position C2 and C3 was reported. [31] To address the regioselectivity issue, many studies were reported on the introduction of a directing-group on the molecular scaffold. In 1978 Trost achieved C-H activation in indole desimmetrization thanks to the presence of a suitable double bond. [32] Baran and Corey, in 2002 took advantage of this approach to synthetize (+)-austamide. [33] De Vries introduced an acetate fragment into aniline and achieved selective *ortho* olefination in good yields. [34]



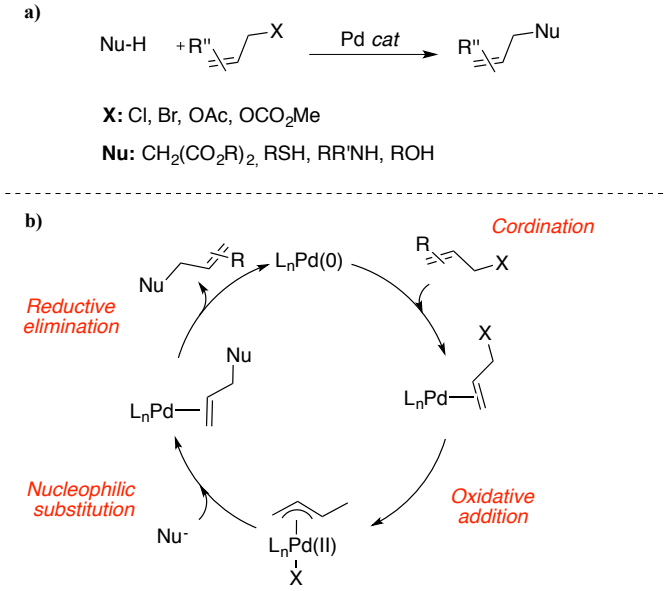
Scheme 5 Examples of C-H activation

Furthermore different studies were reported in C-H activation of *meta* and *para* position of arenes. [35,36] This strategy was than applied to a series of ortho directing groups such as pyridine, carbonates, isoquinolines and many others. [37,38] Directing groups in C-H activation promoted also studies to induce their

removal. A particular case of C-H activation employs norbornene as organic co-catalyst. This is known as the Catellani reaction, originally developed in this University. [39]

2.5 Palladium allylation reactions

Various allylic compounds can react with palladium complexes to form π-allyl complexes that undergo nucleophilic substitution. [40] The allylic substitution is one of the most versatile reaction in organic synthesis. The reaction proceeds via olefin coordination to palladium, followed by oxidative addition forming an η-3 palladium complex. At this point, a soft nucleophile is involved to direct bond formation and form the final product. A hard nucleophile forms a new palladium-nucleophile bond followed by a reductive elimination to achieve the product instead. Palladium allylation are very common, while other transition metals show a major attitude towards linear allylated products. The use of additives such as Lewis acids, Brønsted acids and



Scheme 6 a) General reaction for Tsuji-Trost allylation; **b)** General mechanism for Tsuji-Trost allylation

ligands to activate allylic species allowed to expand the substrate scope. The first palladium catalysed allylic substitution was reported in 1964 by Tsuji, in which an allylic chloride or alcohol were employed with diethylmalonate. [41] Since that allylic alcohols started to be the massively studied. [42] The reaction presents a huge flexibility in term of allylic substrates and nucleophiles as reactants.

2.6 Intramolecular palladium catalysed reactions – synthesis of heterocycles

For a long time, palladium couplings remained limited to intermolecular reactions, but starting from the 1980s an intramolecular version was introduced to achieve heterocyclic compounds. Widespread natural products present at least one heterocycles. The demand of heterocyclic compounds engaged chemists to develop simple and efficient synthetic strategies. In particular, palladium plays a very important role thanks to the wide range of bonds that can be formed. This methodology tolerates a wide range of functional groups, hence protecting groups could be avoided. Furthermore, high stereo- and regioselectivity could be achieved in high yields. The palladium methodology represents an excellent tool in the synthesis of indoles, furans, thiophens, benzoxazoles and thiazoles. [43] One of the most applied intramolecular reaction is the Stille-Kelly coupling. [44] This reaction employs bis(aryl halide) as substrate combined with a distannane reagent to achieve a new carbon-carbon bond yielding stilbenes. This methodology is largely applied to synthetize dihydrophenanthrenes, carbazoles, dibenzofuran and dibezothiophenes. [45,46] In analogy, the Ullman palladium cross-coupling could be applied. [47] An routine type of palladium cross-coupling in heterocycle formation is the Heck reaction. However, high temperatures are requested under classical reaction conditions. Milder conditions were reported

by Jeffery in 1984. [48] He introduced a phase transfer agent employing NBu_4Cl. This allowed to conduce the reaction at 30 °C with high yield and selectivity. These updated conditions are known as *Jeffery condition*.

Indole is present in a myriad of natural products, pharmaceutical agents and in a growing list of polymers. The most famous indole derivatives are serotonin and the amino acid tryptophan. Starting from the 70s, a vast number of synthetic strategies were reported due to the immense importance of indoles.[49] The first palladium coupling was reported in 1977 by Mori and Ban *via* pyrrole annulation. [50] Then, Hegedus in 1977 reported an intramolecular amination of olefins mediated by palladium. [51] Later in 1987, Larock reported an improvement of the Mori and Ban reaction, and in 1996 he reported the cyclization of olefinated tolylamides. [52,53] In 1991 Larock reported the first palladium catalysed hetero-annulation of internal alkynes to achieve a 1,2-substitued indoles. [54] That one is known as the *Larock indole synthesis*.

A large class of bioactive compounds present a nitrogen heterocycle. For this reason, it appears interesting to discover new synthetic organic strategies. An enormous work was focused on the synthesis of pyrroles. Palladium catalyses a multitude of pyrrole synthesis, in particular employing alkynes. [55,56] The first application of palladium catalysis was reported in 1996 by Ohta via β-hydroxy-amines readily available from aminoacids. [57] Another exploited strategy goes through the carbon-nitrogen bond formation. An early example was reported by Trost in 1980 employing allyl acetate derivates and benzyl amines *via* intermolecular annulation reactions. [58] A further improvement into pyrrole synthesis was achieve by intramolecular cyclization. [59,60]

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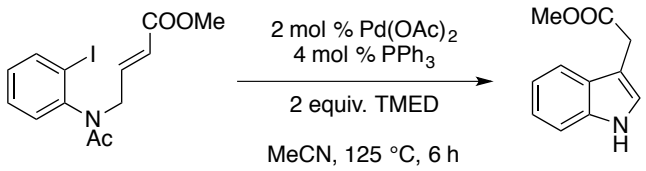

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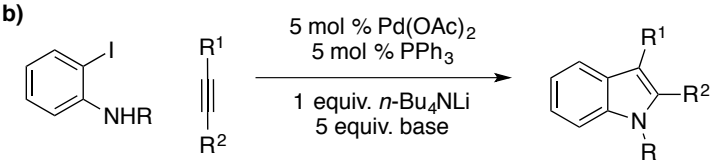

51 - 98 %

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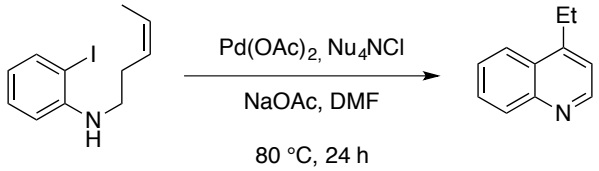

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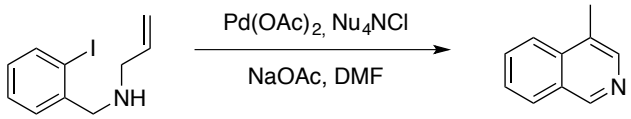

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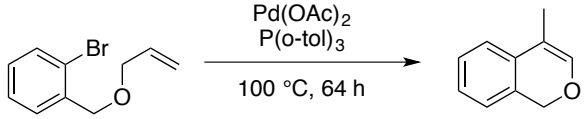

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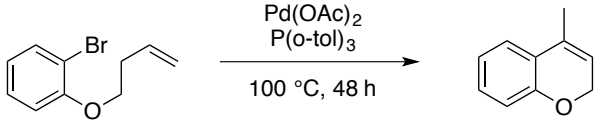


47 %

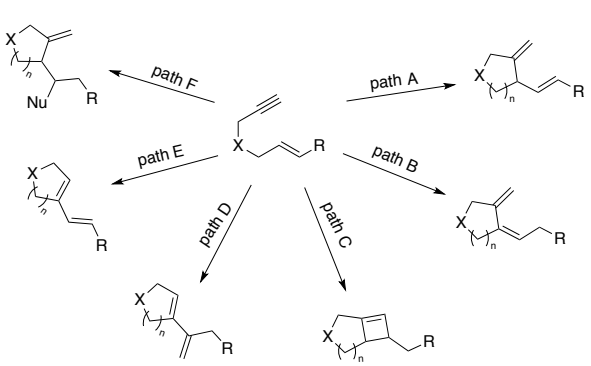
Scheme 7 Examples of palladium cross-coupling in heterocyclies synthesis

Quinolines play an important role in medicinal chemistry. In palladium cross-coupling chemistry the first reported methodology followed the *Jeffery' ligandless* conditions. It was described by Larock and Babu in 1987. [52] These strategies are similar to those already reported by Mori and Ban for the synthesis of indoles.

Furan-containing molecules are found in both natural and pharmaceuticals. The synthesis of benzofurans and furans via palladium chemistry has been an active and prolific field. The most important reaction applied is the intramolecular Heck cross-coupling. In analogy to the synthesis of indoles, Larock employed the *Jeffery' ligandless* conditions for the synthesis of furans through cyclization of ortho-halo vinylphenoles. [61] This cyclization approach could be applied also in the opposite way. Indeed, a halide could be transferred to an allyl fragment to achieve the target product via palladium arylalkylation. Pyrane could be obtained via Heck cross-couling. Heck reported in 1983 the first intramolecualr cyclization. [62]
Although the standard Heck conditions suffer from the presence of sulfur, benzothiophenes and dibenzothiophenes can be obtained via palladium cross-coupling in good yields. [63]

Others important heterocycles can be synthetized via palladium cross-coupling reactions. An application of cross-coupling versatility can be found in total synthesis. [64] Important applications of palladium catalysis in cyclic compounds formation will be present in the following cycloisomerization paragraph.

2.7 Palladium cycloisomerization



Scheme 8 Examples of palladium catalysed cycloisomerization products

In accordance with the green chemistry requirements, chemists are driven to develop suitable synthetic strategies. The core of organic synthesis challenges is represented by the selectivity, as chemo-, regio- and stereoselectivity joint with the development of practical and economical methodologies. Cyclic scaffolds, ubiquitously present in natural products and pharmaceutically active principles, are one of the most important structural motif. This combination of purposes can be accomplished by transition metal catalysed cycloisomerization reactions. [65] Indeed, due to their high versatility, the transition metal catalysed cycloisomerizations abundantly occupy a strategic role in the synthetic field, notably in the total synthesis of natural products. [66] A large number of metals are able to catalyse the cycloisomerization of 1,n-enynes to achieve a vast array of cyclic products under mild conditions and with excellent chemo- and regioselectivity. The fundamental modification and the rapid increase of structural complexity led chemists to strengthen the understanding of their mechanistic aspects.

Starting from the first publication of Trost and Lautens in 1985, 1,n-enynes cycloisometization catalysed by palladium has become one of the most important strategy for the synthesis of functionalized cyclic structures. [67] An extraordinary molecular complexity from linear substrates to (poly)cyclic compounds can be accessed. Different mechanistic pathways can be at work depending on the

choice of the enynes, on the reaction conditions and on the palladium precursor. [68]

The most common palladium catalysed cycloisomerization pathways are shown in Figure 2**.** After complexation of the metal centre by enynes unsaturations, the mechanism can evolve into different ways. Common products in cycloisomerization reaction of 1,n-enynes are 1,3- and 1,4-dienes. These come from the palladacycle pathway. An oxidative cycloaddition occurs to generate the this metallacycle. The regioselectivity in the β-elimination to extract either H_a or H_b protons gave respectively 1,4- or 1,3-dienes. When the rate of β-elimination is hampered by steric effects, direct reductive elimination occurs. That proceeds to the corresponding metastable bicyclobutenes, which can undergo electrocyclic ring opening to 1,3-dienes.

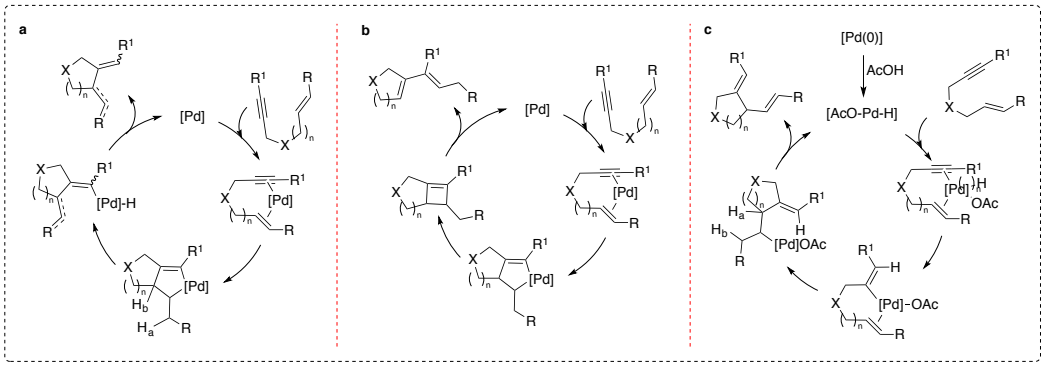
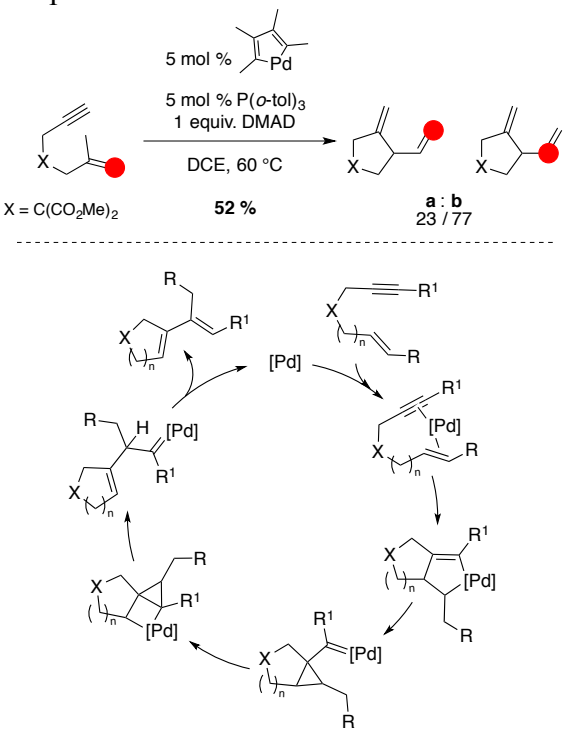


Figure 2 Palladium cycloisomerization mechanism

A further mechanism involves vinylmetal intermediates. Trost in 1994 explained the mechanism. [69] A palladium (0) precatalyst in presence of a carboxylic acid generates a palladium hydride species. An alkyne can insert in the Pd-H bond and generate the vynilpalladium intermediate, which is the active species in the cyclization. The β-elimination can result into either a 1,3- or a 1,4-diene.

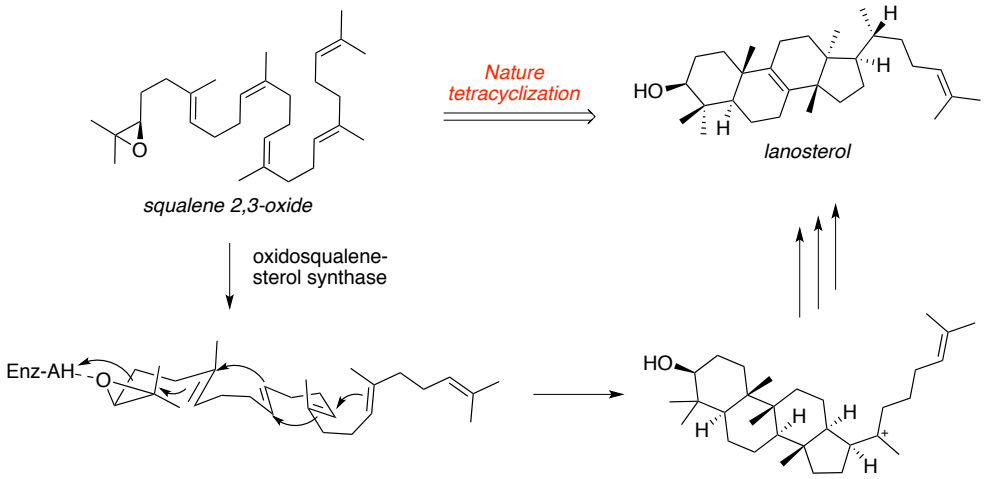
In 1993 Trost, using a labelled 1,6-enyne, recovered a mixture of products. To rationalize this result, he proposed a palladacarbene intermediate. [70]. After the generation of a pallacycle, a rearrangement leads to a cyclopropylcarbene, the successive [2+2] and retro-[2+2] rearrangement lead to the formation of this palladacarbene. A 1,2-shift followed by β-elimination releases the product. [71] This innovative palladium ability was then applied into a cyclization-dimerization during which the cyclopropane could be preserved. [72]



Scheme 9 Enyne cycloisomerization palladium catalysed; Proposed mechanism to explane product **b**

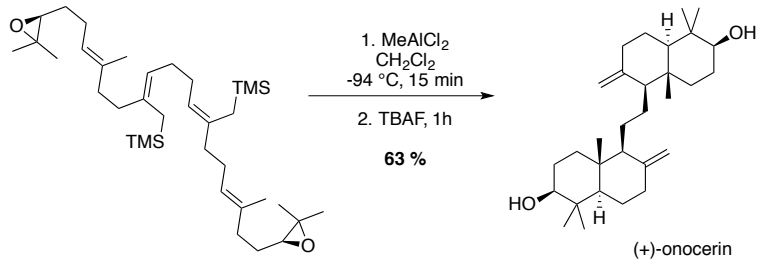
2.8 Domino reactions

The most common organic synthesis approach to complex molecules foresees a step-by-step single bond formation. Nowadays, modern synthesis allows the formation of several bonds in one step. Often these approaches should be entirely carried out without any further reagents or additional catalyst. These type of transformations are called domino or cascade reactions. The domino reaction represents a powerful tool to build up molecular complexity joint to time-resolving synthesis approach. These reactions can be categorized on the base of their reaction mechanism, including cationic, anionic, radical, pericyclic, photochemical and transition metal catalysed. Nevertheless, the distinctions could be achieved on the base of the substrates. Indeed, these transformations can be carried out with a multi-reagents approach or employing a prefunctionalised ones. [73] Nature offers striking examples from the assembly of steroids. [74] More than 100 natural products contain a steroid core that serve for a myriad of biological functions. An example of the ability of nature is represented by the lanosterol synthesis from squalene 2,3 – oxide. Tetracyclizations are indeed fascinating reactions able to deliver a spectacular level of molecular complexity from a suitably tailored, linear reagent.



Scheme 10 Selected example of nature approach to tetracyclization

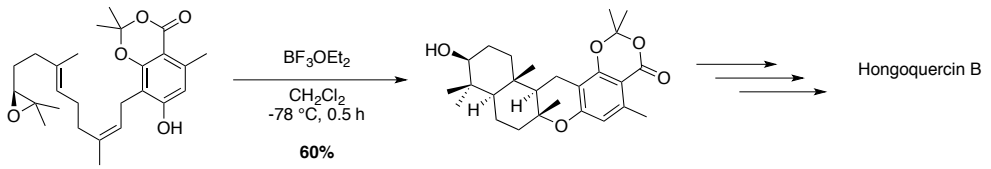
Due to the importance of tetracyclic cores of natural products, chemists investigate strategies to synthetize other bioactive terpenoids via classical organic total synthesis. In order to enhance the molecular complexity as quickly as possible cascade reaction have an important role. An example were reported by Corey in the total synthesis of (+)-α-onorecin, in which a Lewis acid catalyzed tetracyclization built up the tetracyclic product in a single step. [75]



Scheme 11 Selected example of cyclization in total sinthesis

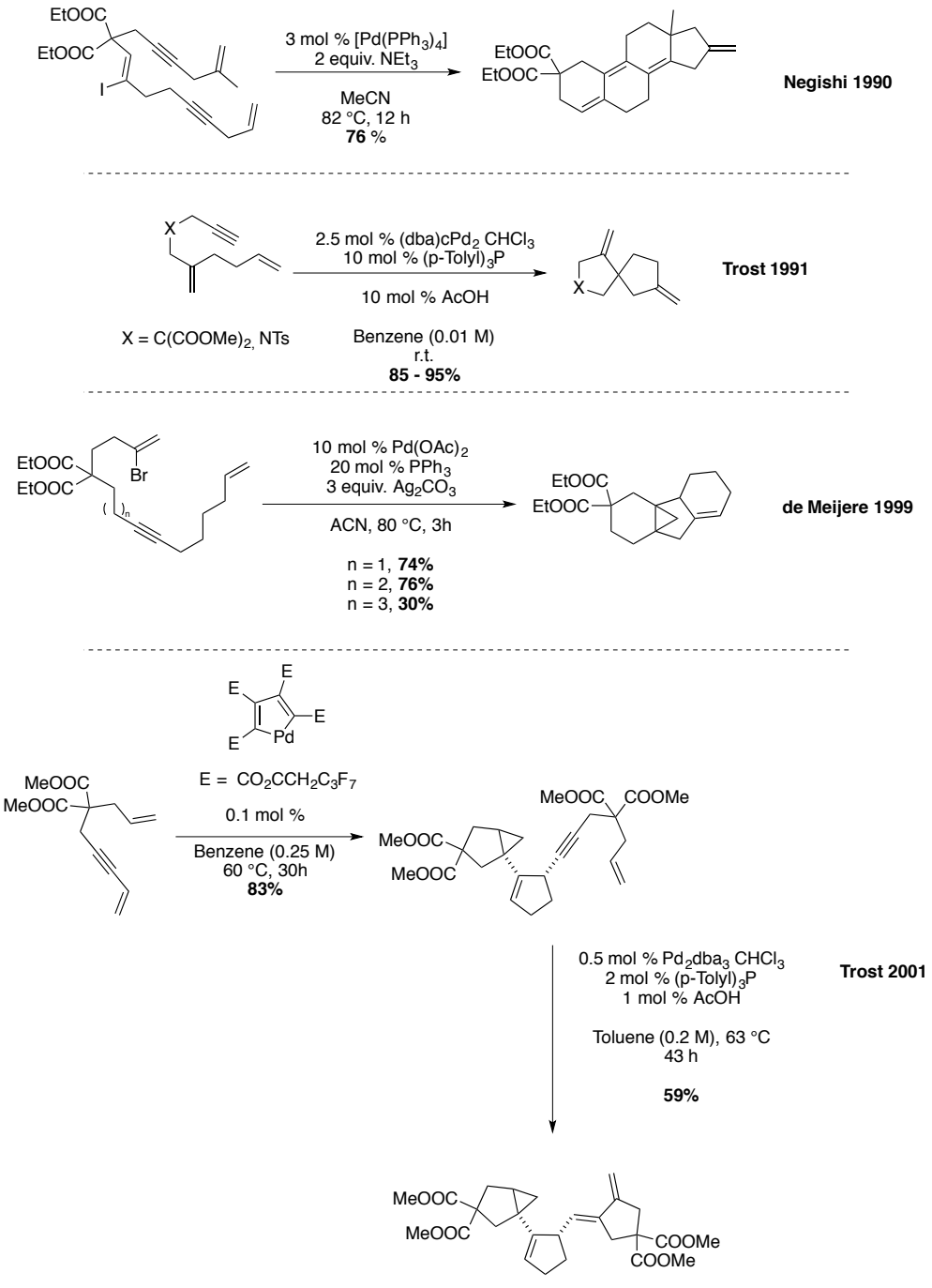
More recently Barret reported the total synthesis of hongoquercin B. The strategy needed nine steps, one of which is a triciyclization reaction of an epoxy-diene.

The stereoisomer of the epoxyide furnishes the control to the all of the four newly created stereocenters.



Scheme 12 Selected example of cyclization in total synthesis

As already discussed, transition metal catalysis represent an important tool for organic chemistry. [76–78] One of the most brilliant examples was reported by the Negishi in 1990. He reported a palladium catalyzed domino reaction to build up a multitude of rings in one step. Starting from a triendiyne substrate in just one step he reported the formation of four cycles. [79] Then, in 1991 Trost reported a polyolefin cyclization to spiro-bycyclic products. [80] De Meijere, in 1999 reported a palladium domino cyclization of dienynes to tetracyclic compounds. [81] An elegant wear of polyunsaturated substrate was presented by Trost in 2001. [72] He reported the formation of polycyclic products through a two-step mechanism reaction, a sequential cycloisomerization/dimerization cascade.

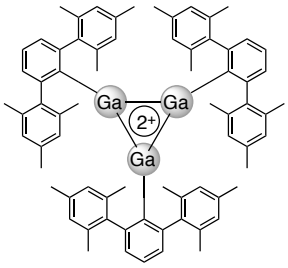


Scheme 13: Selected examples of palladium catalyzed cascade reactions

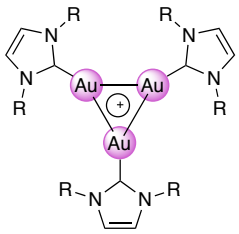
2.9 Metal aromatic palladium clusters

Since its introduction in 1865 by August Kekule the concept of aromaticity fascinated every generation of chemists. The name "aromatic compound" was initially awarded to benzene, its derivatives, and related compounds because of their aroma. [82] Today, the terms "aromatic" and "aromaticity" are used to describe cyclic, planar, and conjugated molecules possessing (4n +2) shared electrons and having specific chemical and structural stability. [83] In recent years, this concept has been advanced from main-group elements to include organometallic compounds with cyclic cores including metal atoms and, in particular, clusters. [84] Aromaticity in transition-metal systems has been discussed particularly in the literature since the discovery of aromaticity in all-metal clusters. [85]

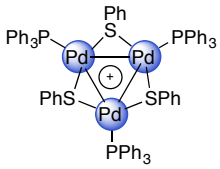
In 1995, Robison reported the first organometallic compound containing an aromatic triangular ring composed by three gallium atoms. [86] Later studies proved the presence of two electrons shared in three *sp*AO that fulfil the 4n+2 rule for π aromaticity. [87] In 2012, Sadighi followed by Bertrand, reported a triangular aromatic monocationic gold complex. [88,89] The cluster presents two electrons in a σ-type MO delocalized over the three metal centers.



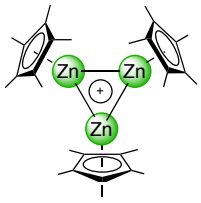
Robison 1995



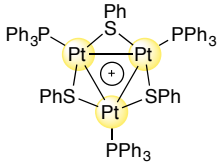
Sadighi 2012



Maestri 2014



Fischer 2015



Maestri 2015

Figure 3 Selected examples of all metal aromatic clusters

A similar type of aromaticity was detected in zinc triangular clusters, as reported by Fischer in 2015. [90]

Recently, all metal aromatic clusters based on palladium and platinum were reported by Maestri. [91,92] These unique clusters present distinct properties. In particular, palladium cluster shows high symmetry (D_{3h} symmetry of core and a C_3 overall symmetry) and a peculiar palladium formal charge ($+^4/_3$). Moreover, this cluster shows a σ-type and π-type MOs delocalized on its three metals. Further DFT investigations reported a largely negative quadrupole moment. On the base of literature, this is a peculiar characteristic of Lewis basic compounds. However, the cluster reports a positive charge and that is synonymous of Lewis acidity. Molecules that present both Lewis acidity and basicity are known to possess a frustrated Lewis pairs (FLP) behaviour. [93]

The FLP character was already known in a wide number of molecular pairs. This interesting property was earlier applied in catalysis such as in hydrogenation reactions, in which FLP species demonstrate the ability to split the hydrogen molecule.

These tripalladium aromatic clusters were recently explored in the semireduction of internal alkynes. [94,95]

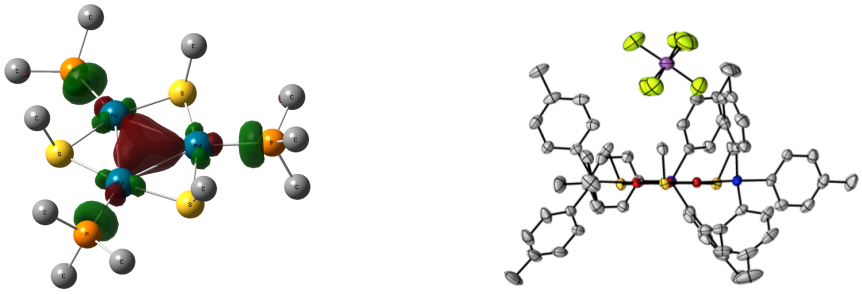


Figure 4 From the right to left: picture of molecular orbital HOMO (dx^2-y^2) and X-Ray ortep of $[Pd_3]^+$

2.10 References

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3 Synthesis of Carbolines

From this chapter: *Org. Lett.* **2018**, *20*, 3220−3224; Gianpiero Cera, Matteo Lanzi, Davide Balestri, Nicola Della Ca', Raimondo Maggi, Franca Bigi, Max Malacria, Giovanni Maestri

3.1 Introduction

Tetrahydro-1H-β-carbolines (THCs) are important cores in organic chemistry due to their presence in many bioactive alkaloids and pharmaceuticals (Figure 5). [96–99]

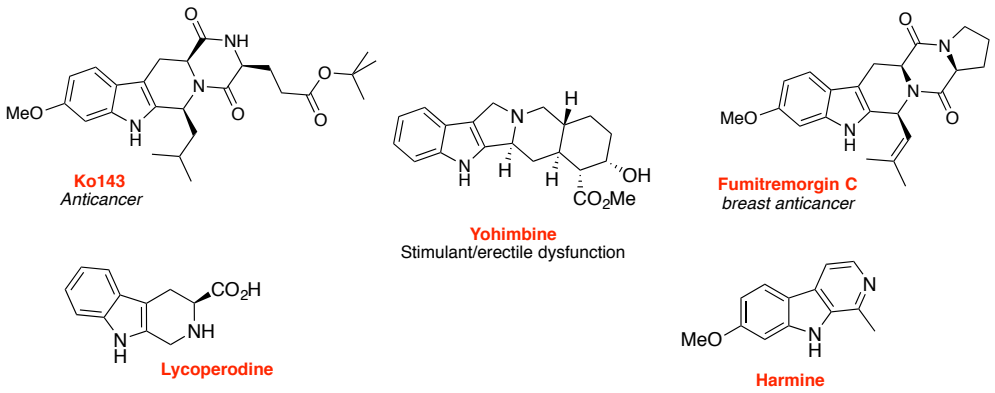
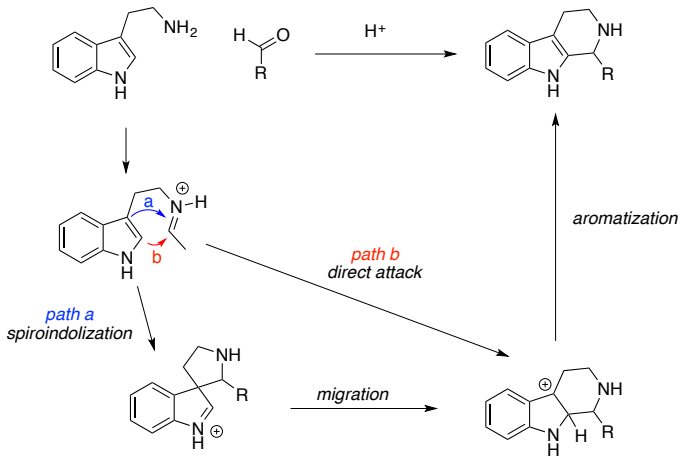


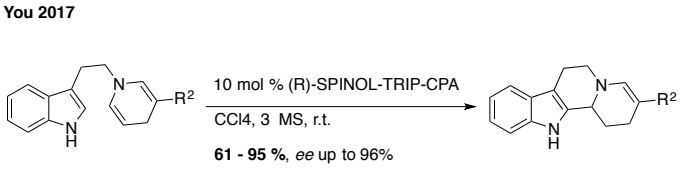
Figure 5 *selected examples of active molecules containing β-carbolines moieties*

Therefore, straightforward synthetic approaches are in high demand. The synthesis of THC analogues traditionally relies on Pictet−Spengler reactions. [100] Reported in 1911 this reaction is nowadays one of the most important reactions for the construction of alkaloids. [101] The reaction employs tryptamines and aldehydes and proceeds through an initial formation of an iminium ion followed by nucleophilic attack by the aryl group and cyclization to achieve the tetrahydro β-carbolines. The nucleophilic attack can occur in position 3 and generates a spiro-intermediate, which can rearrange to obtain the carbolines derivate. The formation of spiro intermediate is fast and reversible. A widespread species, such as a biocatalyst, a Lewis or a Brønsted acid are known to be able to catalyse this reaction. [102,103]



Scheme 14 Example of Pictet−Spengler reaction and mechanism

Enantioselective approaches could rely on either organo- or bioinspired catalysts. Recently, You reported an example of enantioselective Pictet−Spengler chiral phosphoric acid catalysis. However the substrate were prepared through a multistep protocol. [104] Further important approach to tetrahydro β-carbolines are represented by oxidative C−H functionalization. C-H activation with transition metal catalysts and oxidants can show large applications in heterocyclic chemistry. [105–107]

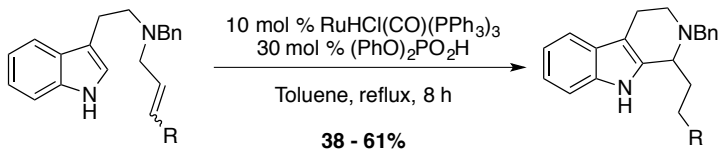


Scheme 15 Selected example of enatioselective Pictet−Spengler

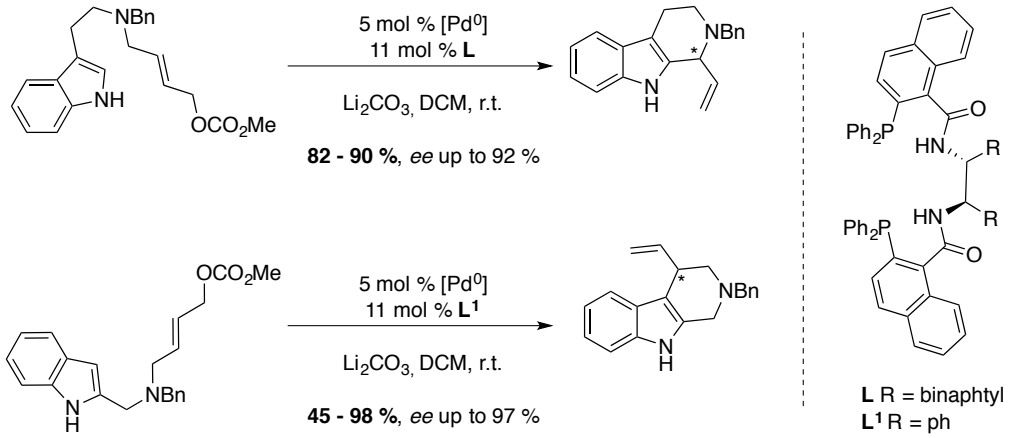
Metal catalysed Pictet−Spengler reactions to THCs are well documented. Transition metal catalysis is an important alternative. Intramolecular hydroarylation of unsaturated substrates such as alkenes, allylic alcohols, and their derivatives are well documented. [108,109] Nielsen engaged allylic amide of tryptamines with ruthenium hydride as catalyst. [110] Derivatives, such as aryl allyl reagents, were prepared via Suzuki cross-coupling. A Palladium protocol

for the synthesis of β- and γ- carbolines was proposed by Bandini in 2006. It involved the intramolecular symmetric allylic alkylations (AAA) employing allyl carbonates derivatives. [111]

Nielsen 2013

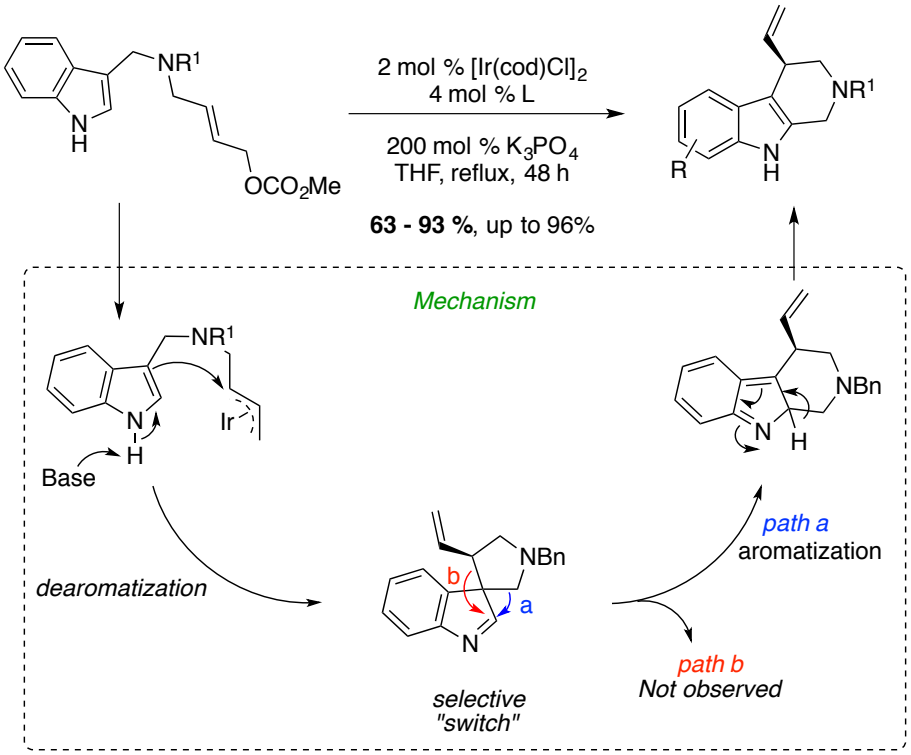


Bandini 2006



Scheme 16 Example of carbolines sinthesis

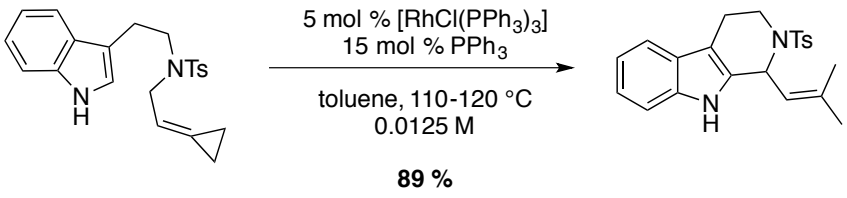
In 2010, You reported the enantioselective synthesis of spiroindolynes catalysed by iridium, which represent, as mentioned before, a plausible intermediate in Pictet−Spengler reaction. [112] Later he took advantage of this method to propose a synthesis of tetrahydrocarbazole. [113] An interesting mechanism to β-carbolines was reported recently, iridium and allyl carbonates evolve through an AAA mechanism leading to the formation of a dearomatized spiroindolynes, this reactive intermediate following then selective "switch" migration. [114]



Scheme 17 Selected example of carbolines synthesis

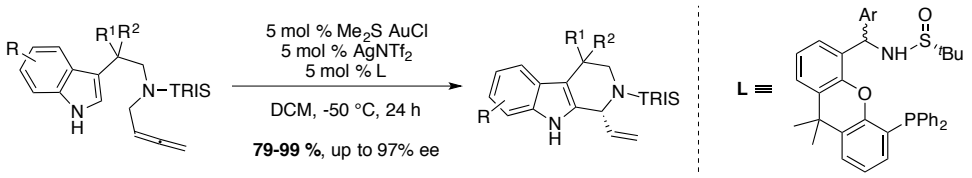
Unfortunately, these protocols suffer from low atom economy either in the preparation of substrates or in the cyclization reaction due to the presence of leaving groups. An important improvement was reported in 2009 by Bandini using a gold catalyst and allyl alcohol derivatives to access tetrahydrocarbazoles. [115]

Shi report the construction of the fused six-member rings through the cycloisomerization of vynilydencyclopropanes using rhodium(I) as catalyst. [116] He exploit their ability to form a diene, which can undergo cyclisation. This protocol needs the synthesis of a vynilydencyclopropanes arm.



Scheme 18 Rhodium approach to carbolines

An important alternative has been recently realized by Zhang developing gold-catalysed allenamide cyclization. [117] However, he reported a wide application of these methodology to terminal allenamides only, and internal allenamides lead to a mixture of products. Moreover, this approach suffers from the inherent challenges of modular allenamide synthesis. [118,119]

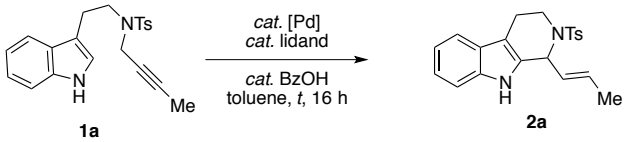


Scheme 19 Example of cycloisomerization of allenes to carbolines

An alternative approach can be observed in the hydroarylation of a triple bond. Their reactivity with soft π-acidic transition metals is well known. In particular, Bandini, Echavarren and Gandon employed gold(I) catalysis, while Beller used platinum(II) as catalyst to achieve the construction of polycycles containing an indole fragment. [120–123]

3.2 Results and discussion

On the base of the precedent works into the synthesis of carbolines, we focused our attention in the cycloisomeriazion of readily available propargylic tryptamines employing a palladium catalyst. The aim of our investigation was the introduction of an easy and handy protocol for the synthesis of tetrahydro β-carbolines that merges the complete atom economy of isomerisation reactions with a straightforward substrate synthesis.



1a **2a**

Entry	[Pd]	Ligand	T [°C]	2a [%]
1	$Pd(PPh_3)_4$	PCy_3	100	38
2	$Pd(PPh_3)_4$	dppe	100	59[b]
3	$Pd(PPh_3)_4$	dppp	100	7[b]
4	$Pd(PPh_3)_4$	dppf	70	45[b]
5	$Pd(PPh_3)_4$	PPh_3	100	71
6	$Pd(PPh_3)_4$	PPh_3	70	70
7	$Pd(dba)_2$	davephos	100	40
8	$Pd(OAc)_2$	PPh_3	100	--
9	$Pd(PPh_3)_4$	PPh_3	70	21[c]
10	$Pd(PPh_3)_4$	johnphos	70	69
11	$Pd(PPh_3)_4$	*t*-BuXphos	70	48
12	$Pd(PPh_3)_4$	$(4\text{-}OMeC_6H_4)_3P$	70	18
13	$Pd(PPh_3)_4$	$(4\text{-}FC_6H_4)_3P$	70	--
14	$Pd(PPh_3)_4$	MA	70	--[d]
15	***$Pd(PPh_3)_4$***	***PPh_3***	***100***	***78[e]***

[a] Reaction conditions: **1a** (0.20 mmol, [Pd] (5 mol %), Ligand (10 mol %), BzOH (30 mol %), toluene (0.1 M), yields of isolated product. [b] Ligand (5 mol %). [c] THF (0.1 M) as solvent. [d] MA = maleic anhydride. [e] [Pd] (10 mol %), PPh_3 (20 mol %). dppe = 1,2-Bis(diphenylphosphino)ethane. dppp = 1,3-Bis(diphenylphosphino)propane. dppf = 1,1′-Bis(diphenylphosphino)ferrocene.

We took advantage to the ability of palladium(0) and carboxylic acids to generate a palladium hydride species that can allow insertion into triple bonds. [124–126] At

first, we investigate the phosphine ligands, employing **1** as substrate. THC **2a** was isolated as a single *E*-isomer in 38% yield using PCy_3. Bidentate phosphines yielded **2a** with slightly better performances. The use of cheaper PPh_3 promoted the catalytic transformation with moderate yields and high chemoselectivity, even at lower temperature. Then we investigated the palladium source. $Pd(dba)_2$ could be applicable, although to a lower extent, even though, a Pd(II) precursor, such as the popular $Pd(OAc)_2$, was not a suitable catalyst for this transformation. [127–132] Buchwald's ligands and substituted triarylphosphine analogues were unable to improve the catalytic system. [126] Hence, **2a** was isolated in 78% yield by increasing the catalyst loading. The reaction without benzoic acid provided traces of **2a**, highlighting the crucial role of the former. In all cases, we observed complete control of the alkene configuration, retrieving **2a** as a single *E*-isomer.

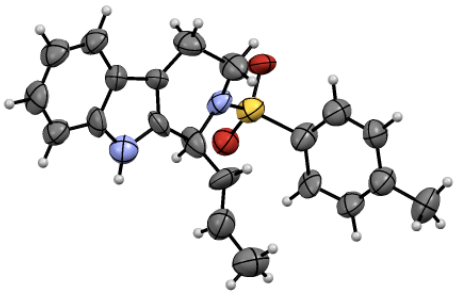
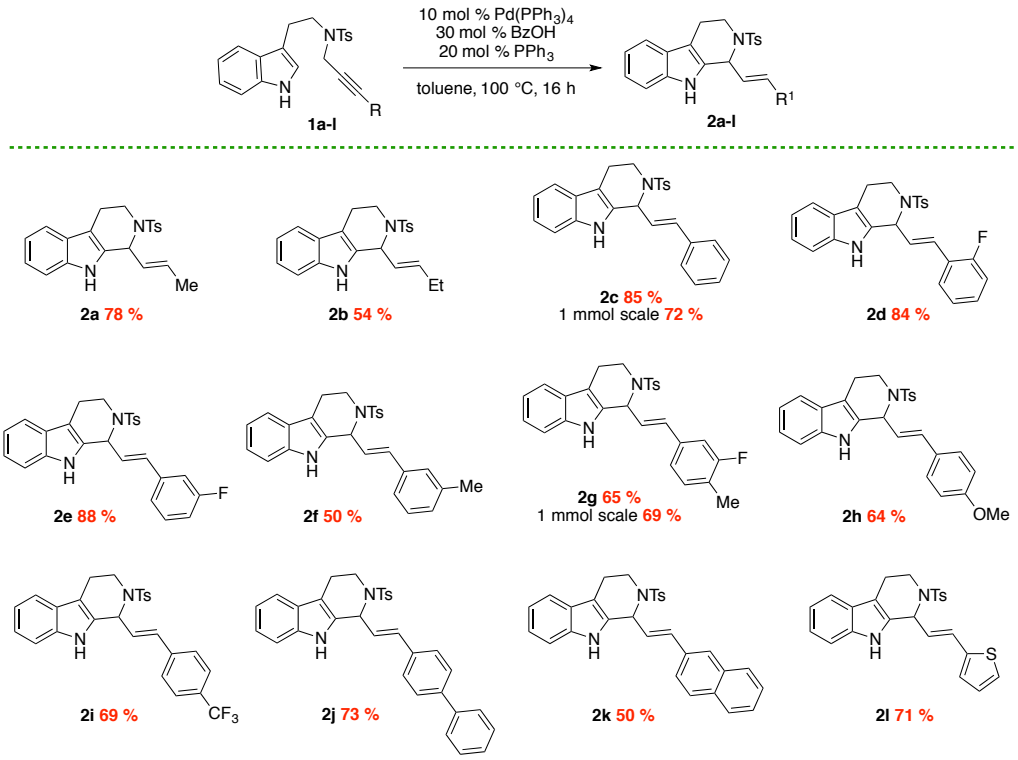


Figure 6: Single cristal XRay diffraction of **2a**

We than studied the generality of the reaction. A family of diversely functionalized propargylic tryptamines **1** was then submitted to the optimized catalytic system.

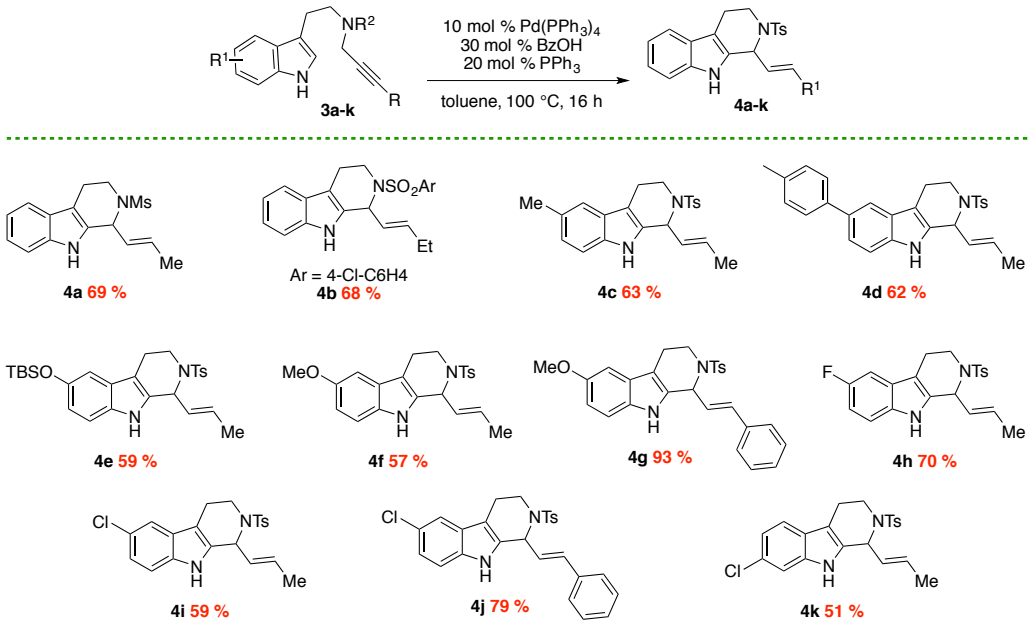


Scheme 20 Scope of propargyl fragment

Alkyl- and arylalkyne derivatives were tolerated, leading to the corresponding products **2b-c** in 54 and 85% yields, respectively. A broad family of 3-arylprop-2-yn-1-ylindole derivatives **1** was efficiently converted to THCs **2**. Thus, the method is suitable for the synthesis of various fluorinated THCs. Substrates bearing EWGs performed better with respect to the corresponding electron-rich ones. Tryptamine derivatives bearing biphenyls, naphthalenes, and heteroarenes, such as thiophene, delivered the corresponding THCs in good yields (**2j–l**, 50−73%). Reactions involving arylalkynes (**2c–l**) deliver the desired products only, and unreacted starting materials can be recovered by chromatography.

Then, we studied substituted tryptamines. Protection of tryptamine with either methanesulfonyl (Ms) or *p*-Cl-benzensulfonyl did not affect the outcome of the

catalytic reaction (**4a-4b**).



Scheme 21 Scope of indole substitution

Electron-donating functional groups such as alkyl, aryl, silyl ethers and ethers at the C(5)- position of the indole were well tolerated, delivering THCs **4c - g** with good to excellent yields (57−93%). The method allowed the synthesis of THCs **4h** − **k** with electron-withdrawing groups located at the C(5)- and C(6)-position with moderate to good yields (51−79%).

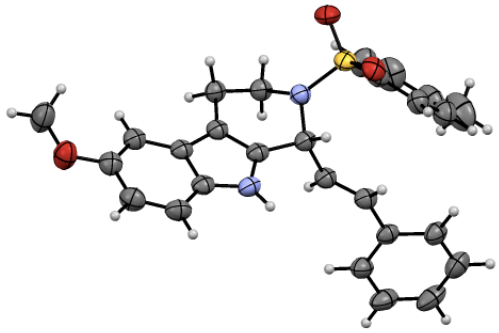
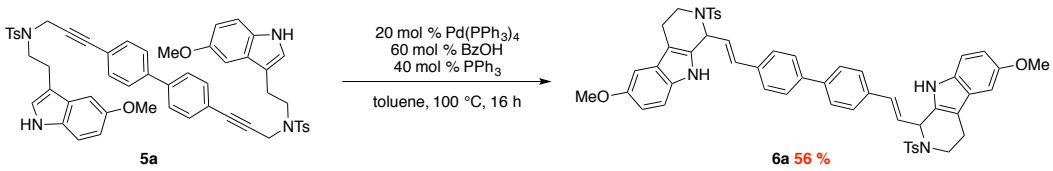


Figure 7: Single cristal XRay diffraction of **4g**

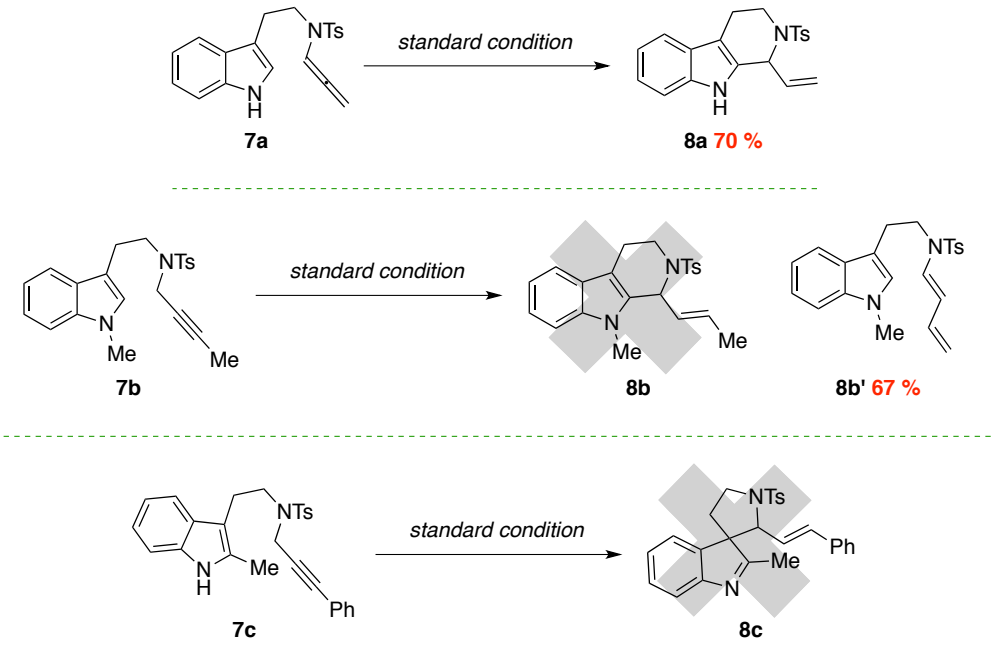
The robustness of the sequence was further mirrored by the synthesis of a symmetrical THC dimer. Noteworthy, the synthesis of **4l** proceeds smoothly with high chemoselectivity and a synthetically useful yield (56%).



Equation 1 Sinthesis of dimeric THC

Then, different experiments were carried out to rationalize the reaction mechanism and gain insights on its complete chemo- and site-selectivities. THC **4m** was isolated in 70% yield using allenamide **3m** under typical reaction conditions. This result is consistent with the intermediate formation of an allenamide in the sequence. Then, the influence of indole N-substitution was investigated.

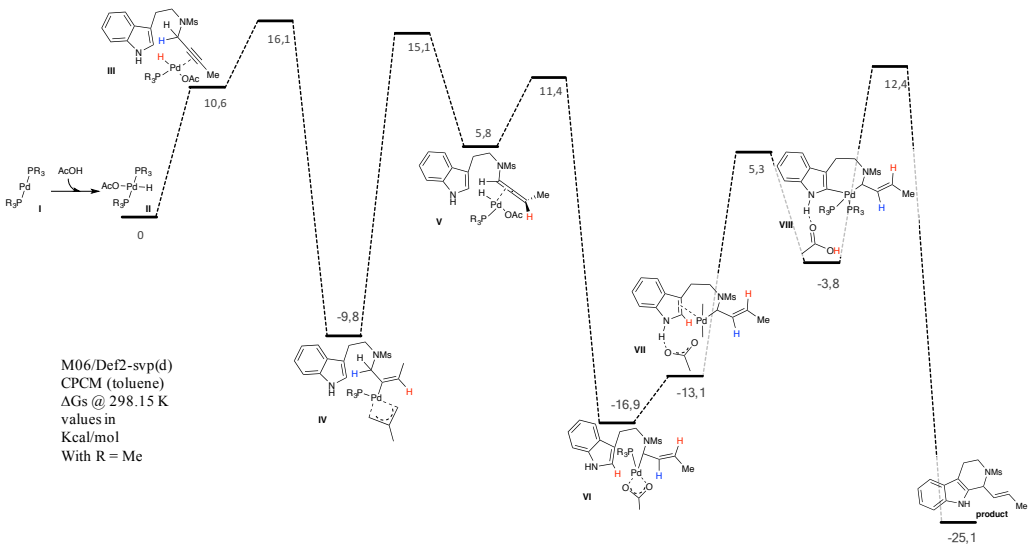
We observed the formation of acyclic diene **4n′** and no traces of THC **4n** by testing precursor **3n**. This result shows that the free N−H of the indole is crucial for the annulation step and shows once more the virtues of a protecting-group free synthesis. [133] Finally, the attempted intramolecular dearomatization of propargylic precursor **3o**, in which the indole C(2) is substituted with a methyl group, failed to provide any product. [134] This result was highly unexpected on the basis of the literature precedents and led us hypothesize that a C−H activation step could operate in our case. We are unawere of the literature precedents on C−H activation/alkylation at C(2) of unprotected indoles. [135–139]



Scheme 22 Experimental mechanism investigation

Thus, we resorted to DFT modelling to solve the riddle. The investigation began using the M06 functional in combination with either lacvp(d) and Def2-svp(d) basis sets, which proved to be reliable methods to describe elaborate palladium-catalysed sequences (Scheme 19). [140–142] Complete pathways were modelled with PMe_3 as ligand both in the gas phase and using toluene as implicit solvent to reduce further the odds of modelling artefacts. Different functionals were also tested and the key steps were reoptimized with PPh_3. Overall, coherent results were obtained in all cases, which led us to propose the mechanism of Scheme 23 to account for the formation of THC **2** in these sequences. A reaction of the carboxylic acid with Pd(0) complex **I** can deliver trans-Pd(II) hydride **II**. Its cis-peer is less stable and furthermore requires a higher barrier too. Endoergonic phosphine replacement by the substrate yields complex **III**, which evolves to vinyl species **IV** via migratory insertion. Barriers for this step were expectedly low (between +2.8 and +6.8 kcal/mol among the different models). The

subsequent β-elimination affords allenamide complex **V**. This proved to be the most energy-demanding barrier of the whole sequence because of the limited rotational flexibility of the allylic methylene (ΔG of +24.9 kcal/mol; up to +28.1 at the B3LYP level). Complex **V** is more stable than its alkyne peer **III** (by −4.8 kcal/mol). This suggests that allenamides bind Pd(II) hydrides more strongly than an internal alkyne. A second insertion into the Pd−H bond gives allyl complex **VI** through a low barrier process (+5.2 kcal/mol in ΔG). Replacement of the acetate ligand by phosphine provides complex **VII**, in which the metal presents a slipped η^2-indole coordination, and the carboxylate is engaged in hydrogen bonding with the indole N−H group. This is crucial to favor the sequential C−H activation, which occurs through an outer-sphere CMD pathway [143–149] (barriers of +18.2 and +18.8 kcal/mol in ΔG with PMe_3 and PPh_3, respectively). This is consistent with the positive role of additional ligands on yield. It is worth noting that direct C−H activation of indole is, on the contrary, usually prevented by the presence of a free N−H group, which sunk the basicity of metal-bound carboxylates via hydrogen bonding.



Scheme 23 Most favourable modelled mechanism

Modeling an inner-sphere CMD indeed provided higher barriers (+29.2 kcal/mol in ΔG). Try as we might, we failed to obtain any stationary point for Pictet−Spengler-like pathways from either complex **V** or **VI**. Scans of these pathways show a linear increase of E only (up to above 40 kcal/mol), suggesting that indole dearomatization does not lead to any stable intermediate in these cases. These results parallel recent computational ones on C-palladations previously thought to occur via electrophilic aromatic substitutions. [150]

Heck-like insertion on indole from **VII** provided a sky-high barrier of +50.5 kcal/mol. Taken together within the framework of the energy span model, [151] these results strongly suggest that indole functionalization occurs via C−H activation in this sequence. The results also highlight the dual nature of the carboxylic acid in this cascade. It initially serves to generate the Pd hydride that triggers alkyne isomerization. The resulting carboxylate then becomes crucial as well. It plays the role of a base assisting the metal in the C−H activation, therefore acting in a catalytic fashion. The desired product is eventually released by C−C

reductive elimination from metallacycle **VIII**. This step has a barrier comparable to those of similar Pd(II) complexes (+16.2 kcal/mol in ΔG).

3.3 Conclusion

We present the first catalytic synthesis of tetrahydrocarbolines from propargylic tryptamines by means of palladium and carboxylic acid joint catalysis. The method combines interesting synthetic features with unexpected mechanistic findings. We anticipate that the latter will produce ample future developments of indole chemistry in C−H activation sequences.

3.4 Experimental section

General procedure A for the synthesis of reagents: In a Schlenk flask, to a solution of tryptamine (1.0 equiv), K_2CO_3 (1.5 equiv) in acetone (10 ml), the corresponding propargyl bromide derivative (1.5 equiv) was added dropwise. Subsequently, the mixture was placed in a pre-heated oil bath at 50 °C and stirred overnight. After completion, the reaction mixture was cooled down to room temperature and sat. NH_4Cl (15 ml) was added. The mixture was extracted with EtOAc (3 x 15 ml) and 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.

General procedure B for the synthesis of tetrahydro-1*H*-pyrido[3,4-*b*]indole: In an oven dried tube, **1** (0.20 mmol), $Pd(PPh_3)_4$ (0.02 mmol), PPh_3 (0.04 mmol) and BzOH (0.06 mmol) were added sequentially and purged with nitrogen three times. Subsequently, toluene (1.0 ml, 0.2 M) was added under N_2 atmosphere and the tube placed in a pre-heated oil bath at 100 °C. After completion (16 hs), the reaction mixture was cooled down at room temperature and CH_2Cl_2 (10 ml) was added. The mixture was concentrated under reduced pressure and the crude purified by chromatography on silica gel.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-4-methyl-*N*-(pent-2-yn-1-yl)benzenesulfonamide (1b)**: The representive procedure **A** was followed using *N*-[2-(1*H*-Indol-3-yl)ethyl]-4-methylbenzenesulfonamide (314 mg, 1.0 mmol) and 1-bromopent-2-yne (220 mg, 1.5 mmol). Purification by chromatography on silica gel yielded **1b** (250 mg, 66%) as a white solid. M. p. = 153.5 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (bs, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 1H),

7.14-7.11 (m, 2H), 4.17 (s, 2H), 3.53 (t, *J* = 7.9 Hz, 2H), 3.10 (t, *J* = 7.9 Hz, 2H), 2.42 (s, 3H), 2.01-1.93 (m, 2H), 0.94 (t, *J* = 7.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2 (C_q), 136.2 (C_q), 136.1 (C_q), 129.3 (CH), 127.8 (CH), 127.3 (CH), 122.2 (C_q), 122.1 (CH), 119.4 (CH), 118.7 (CH), 112.5 (C_q), 111.2 (CH), 87.6 (C_q), 72.0 (C_q), 46.8 (CH_2), 37.2 (CH_2), 24.3 (CH_2), 21.5 (CH_3), 13.5 (CH_3), 12.2 (CH_2). **(ESI) MS** calcd for $C_{22}H_{25}N_2O_2S$ $[M+H]^+$ 381.16 found 381.25.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (1c)**: The representive procedure **A** was followed using *N*-[2-(1*H*-Indol-3-yl)ethyl]-4-methylbenzenesulfonamide (314 mg, 1.0 mmol) and (3-bromoprop-1-yn-1-yl)benzene (290 mg, 1.5 mmol). Purification by chromatography on silica gel yielded **1c** (296 mg, 69%) as a white solid. M. p. = 108.1 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (bs, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.34-7.18 (m, 6H), 7.16-7.08 (m, 4H), 4.44 (s, 2H), 3.62 (t, *J* = 7.4 Hz, 2H), 3.17 (t, *J* = 7.4 Hz, 2H), 2.35 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4 (C_q), 136.2 (C_q), 135.9 (C_q), 131.6 (CH), 129.5 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 127.3 (C_q), 122.3 (CH), 122.2 (C_q), 122.1 (CH), 119.5 (CH), 118.7 (CH), 112.3 (C_q), 111.2 (CH), 85.8 (C_q), 82.0 (C_q), 47.1 (CH_2), 37.6 (CH_2), 24.4 (CH_2), 21.4 (CH_3). **(ESI) MS** calcd for $C_{26}H_{25}N_2O_2S$ $[M+H]^+$ 429.16 found 429.25.

***N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-[3-(2-fluorophenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (1d)**: The representative procedure **A** was followed using *N*-[2-(1*H*-indol-3-yl)ethyl]methanesulfonamide (300 mg, 0.95 mmol) and 1-(3-bromoprop-1-yn-1-yl)-2-fluorobenzene (224 mg, 1.1 mmol). Purification by chromatography on silica gel yielded **1d** (140 mg, 33 %) as a yellow pale solid. M. p. = 125.4 °C. **^{1}H NMR** (300 MHz, $CHCl_3$) δ 8.03 (brs, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 10H), 7.51–6.91 (m, 5H), 4.44 (s, 1H), 3.59

(t, *J* = 7.8 Hz, 1H), 3.14 (t, *J* = 7.9 Hz, 1H), 2.29 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ162.7 (d, *J* = 252.1 Hz, C_q), 143.4 (C_q), 136.2 (C_q), 135.7 (C_q), 133.4 (C_q), 130.2 (d, *J* = 7.8 Hz, CH), 129.4 (CH), 127.7 (CH), 127.3 (CH), 123.7 (d, *J* = 3.7 Hz, CH), 122.2 (CH), 122.1 (CH), 119.4 (CH), 118.7 (CH), 115.4 (d, *J* = 20.8 Hz, CH), 112.3 (C_q), 111.1 (CH), 110.8 (d, *J* = 15.8 Hz, C_q), 87.3 (d, *J* = 3.3 Hz, C_q), 79.1 (C_q), 47.1 (CH_2), 37.6 (CH_2), 24.3 (CH_2), 21.3 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ-109.9 Hz. **(ESI) MS** calcd for $C_{26}H_{23}FN_2NaO_2S$ $[M+Na]^+$ 469.14 found 469.17.

***N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-[3-(3-fluorophenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (1e):** The representative procedure **A** was followed using *N*-[2-(1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (423 mg, 1.2 mmol) and 1-(3-bromoprop-1-yn-1-yl)-3-fluorobenzene (281 mg, 1.3 mmol). Purification by chromatography on silica gel yielded **1e** (410 mg, 76 %) as a white solid. M. p. = 109.4 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (brs, 1H), 7.80 (d, *J* = 7.9 Hz, 2H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 8.3 Hz, 4H), 7.18 – 6.97 (m, 3H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 9.5 Hz, 1H), 4.42 (s, 2H), 3.63 (t, *J* = 7.7 Hz, 2H), 3.16 (t, *J* = 7.7 Hz, 2H), 2.37 (s, 3H). **^{13}C NMR** (75 MHz, $CHCl_3$) δ162.1 (d, *J* = 246.5 Hz, C_q), 143.5 (C_q), 136.2 (C_q), 135.8 (C_q), 129.7 (d, *J* = 8.7 Hz, CH), 129.5 (CH), 127.7 (CH), 127.3 (d, *J* = 2.7 Hz, CH), 127.2 (C_q), 123.9 (d, *J* = 9.6 Hz, C_q), 122.3 (CH), 122.0 (CH), 119.4 (CH), 118.5 (CH), 118.3 (d, *J* = 24.8 Hz, CH), 115.7 (d, *J* = 21.2 Hz, CH), 112.1 (C_q), 111.3 (CH), 84.4 (C_q), 83.0 (C_q), 47.1 (CH_2), 37.4 (CH_2), 24.3 (CH_2), 21.2 (CH_3). **^{19}F NMR** (376 MHz, $CHCl_3$) δ -112.9 Hz. **(ESI) MS** calcd for $C_{26}H_{24}FN_2O_2S$ $[M+H]^+$ 447.15 found 447.13.

***N*-[2-(1*H*-indol-3-yl)ethyl]-4-methyl-*N*-[3-(*m*-tolyl)prop-2-yn-1-yl]benzenesulfonamide (1f):** The representative procedure **A** was followed

using *N*-[2-(1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (423 mg, 1.2 mmol) and 1-(3-bromoprop-1-yn-1-yl)-3-methylbenzene (276 mg, 1.3 mmol). Purification by chromatography on silica gel yielded **1f** (459 mg, 86 %) colourless oil. **^{1}H NMR** (400 MHz, $CHCl_3$) δ 8.06 (brs, 1H), 7.78 (d, *J* = 7.7 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.26-7.04 (m, 7H), 6.92 (s, 2H), 4.41 (s, 2H), 3.60 (dd, *J* = 9.5, 6.0 Hz, 2H), 3.16–3.12 (m, 2H), 2.34 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 137.8 (C_q), 136.2 (C_q), 135.9 (C_q), 132.1 (CH), 129.5 (CH), 129.3 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.3 (C_q), 122.2 (CH), 122.0 (CH), 122.0 (C_q), 119.4 (CH), 118.7 (CH), 112.3 (C_q), 111.2 (CH), 85.9 (C_q), 81.5 (C_q), 47.0 (CH_2), 37.5 (CH_2), 24.3 (CH_2), 21.4 (CH_3), 21.1 (CH_3). **(ESI) MS** calcd for $C_{27}H_{26}N_2NaO_2S$ $[M+Na]^+$ 465.16 found 465.19.

***N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-[3-(3-fluoro-4-methylphenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (1g):** The representive procedure **A** was followed using *N*-[2-(1*H*-Indol-3-yl)ethyl]-4-methylbenzenesulfonamide (314 mg, 1.0 mmol) and 4-(3-bromoprop-1-yn-1-yl)-2-fluoro-1-methylbenzene (337 mg, 1.5 mmol). Purification by chromatography on silica gel yielded **1g** (370 mg, 80%) as a yellow solid. M. p. = 120.5 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (bs, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.25-7.19 (m, 1H), 7.14-7.04 (m, 3H), 6.83 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.68 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.42 (s, 2H), 3.65-3.58 (m, 2H), 3.20-3.12 (m, 2H), 2.38 (s, 3H), 2.26 (d, *J* = 1.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6 (d, *J* = 246 Hz, C_q), 143.6 (C_q), 136.3 (C_q), 135.9 (C_q), 131.2 (d, *J* = 6 Hz, CH), 129.6 (CH), 127.8 (CH), 127.3 (C_q), 127.1 (d, *J* = 3 Hz, CH), 125.9 (d, *J* =17 Hz, C_q), 122.3 (CH), 122.1 (CH), 121.1 (d, *J* = 9 Hz, C_q), 119.5 (CH), 118.7 (CH), 118.0 (d, *J* = 23 Hz, C_q), 112.1 (CH), 111.3 (CH), 84.7 (C_q), 82.1 (C_q), 47.1 (CH_2), 37.5 (CH_2), 24.4 (CH_2), 21.4 (CH_3), 14.5 (d, *J* = 4 Hz, CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.1 Hz. **(ESI) MS** calcd for $C_{27}H_{26}FN_2O_2S$ $[M+H]^+$ 461.17 found 461.19.

***N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-[3-(4-methoxyphenyl)prop-2-yn-1-yl]-4 methylbenzenesulfonamide (1h):** The representative procedure **A** was followed using *N*-[2-(1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (423 mg, 1.2 mmol) and 1-(3-bromoprop-1-yn-1-yl)-4-methoxybenzene (360 mg, 1.6 mmol). Purification by chromatography on silica gel yielded **1h** (480 mg, 87 %) as a white solid. M. p. = 117.2 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (brs, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.22 (q, *J* = 7.1 Hz, 3H), 7.07 (dd, *J* = 9.6, 7.4 Hz, 4H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.40 (s, 2H), 3.80 (s, 3H), 3.59 (dd, *J* = 9.3, 6.5 Hz, 2H), 3.14 (dd, *J* = 9.3, 6.3 Hz, 2H), 2.34 (s, 3H). **^{13}C NMR** (75 MHz, $CHCl_3$) δ 159.6 (C_q), 143.3 (C_q), 136.2 (C_q), 136.0 (C_q), 133.0 (CH), 129.4 (CH), 127.7 (CH), 127.3 (C_q), 122.2 (CH), 122.0 (CH), 119.4 (CH), 118.7 (CH), 114.3 (C_q), 113.7 (CH), 112.3 (C_q), 111.2 (CH), 85.6 (C_q), 80.5 (C_q), 55.3 (CH_3), 47.0 (CH_2), 37.6 (CH_2), 24.3 (CH_2), 21.4 (CH_3). **(ESI) MS** calcd for $C_{27}H_{26}N_2NaO_3S$ $[M+Na]^+$ 481.16 found 481.06.

***N*-([2-(1*H*-Indol-3-yl)ethyl]-4-methyl-*N*-[3-(4-(trifluoromethyl)phenyl]prop-2-yn-1 yl) benzenesulfonamide (1i):** The representive procedure **A** was followed using *N*-[2-(1*H*-Indol-3-yl)ethyl]-4-methylbenzenesulfonamide (314 mg, 1.0 mmol) and 1-(3-bromoprop-1-yn-1-yl)-4-(trifluoromethyl)benzene (396 mg, 1.5 mmol). Purification by chromatography on silica gel yielded **1i** (386 mg, 78%) as a yellow solid. M. p. = 125.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (bs, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.27-7.19 (m, 3H), 7.14 (s, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 4.44 (s, 2H), 3.63 (t, *J* = 7.8 Hz, 2H), 3.17 (d, *J* = 7.8 Hz, 2H), 2.35 (s, 3H). **^{13}C NMR** (101 MHz,

$CDCl_3$) δ 143.6 (C_q), 136.3 (C_q), 135.8 (C_q), 131.8 (CH), 130.2 (d, *J* = 33 Hz, C_q), 129.6 (CH), 127.8 (CH), 127.3 (C_q), 126.0 (C_q), 125.2 (CH), 124.1 (d, *J* = 272 Hz, C_q), 122.4 (CH), 122.2 (CH), 119.5 (CH), 118.6 (CH), 112.2 (C_q), 111.4 (CH), 84.7 (C_q), 84.4 (C_q), 47.2 (CH_2), 37.5 (CH_2), 24.4 (CH_2), 21.4 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ 62.9 Hz. **(ESI) MS** calcd for $C_{27}H_{24}F_3N_2O_2S$ $[M+H]^+$ 497.15 found 497.22.

***N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-{3-([1,1'-biphenyl]-4-yl)prop-2-yn-1-yl}-4-methylbenzenesulfonamide (1j):** The representative procedure **A** was followed using *N*-[2-(1*H*-indol-3-yl)ethyl]methanesulfonamide (300 mg, 0.95 mmol) and 4-(3-bromoprop-1-yn-1-yl)-1,1'-biphenyl (285 mg, 1.05 mmol). Purification by chromatography on silica gel yielded **1j** (294 mg, 61 %) as a white solid. M. p. = 129.3 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (brs, 1H), 7.78 (d, *J* = 7.9 Hz, 2H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.49–7.43 (m, 4H), 7.39–7.36 (m, 2H), 7.26–7.14 (m, 6H), 7.07 (t, *J* = 7.5 Hz, 1H), 4.43 (s, 2H), 3.62–3.58 (m, 2H), 3.17–3.13 (m, 2H), 2.33 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4 (C_q), 141.2 (C_q), 140.1 (C_q), 136.2 (C_q), 135.8 (C_q), 131.9 (CH), 129.5 (CH), 128.9 (CH), 127.8 (CH), 127.7 (CH), 127.3 (C_q), 127.0 (CH), 126.8 (CH), 122.2 (CH), 122.1 (CH), 121.0 (C_q), 119.5 (CH), 118.7 (CH), 112.3 (C_q), 111.2 (CH), 85.6 (C_q), 82.6 (C_q), 47.0 (CH_2), 37.6 (CH_2), 24.3 (CH_2), 21.4 (CH_3). **(ESI) MS** calcd for $C_{23}H_{28}KN_2O_2S$ $[M+K]^+$ 543.15 found 543.14.

***N*-[2-(1*H*-indol-3-yl)ethyl]-4-methyl-*N*-[3-(naphthalen-2-yl)prop-2-yn-1-yl]benzenesulfonamide (1k):** The representative procedure **A** was followed using *N*-[2-(1*H*-indol-3-yl)ethyl]methanesulfonamide (290 mg, 0.92 mmol) and 2-(3-bromoprop-1-yn-1-yl)naphthalene (230 mg, 0.94 mmol). Purification by chromatography on silica gel yielded **1k** (434 mg, 98 %) as a white solid. M. p. = 105.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (brs, 1H), 7.81–7.79 (m, 3H),

7.73–7.66 (m, 3H), 7.61 (s, 1H), 7.51–7.48 (m, 2H), 7.37–7.35 (m, 1H), 7.23–7.13 (m, 5H), 7.07–7.03 (m, 1H), 4.46 (s, 2H), 3.66–3.62 (m, 2H), 3.17 (t, *J* = 8.0 Hz, 2H), 2.28 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4 (C_q), 136.2 (C_q), 135.8 (C_q), 132.7 (C_q), 132.7 (C_q), 131.5 (CH), 129.5 (CH), 128.0 (2 CH), 127.7 (2 CH), 127.7 (CH), 127.5 (CH), 127.2 (C_q), 126.8 (CH), 126.6 (CH), 122.3 (CH), 122.0 (CH), 119.3 (CH), 118.6 (C_q), 112.1 (C_q), 111.2 (CH), 86.0 (C_q), 82.2 (C_q), 47.1 (CH_2), 37.6 (CH_2), 24.3 (CH_2), 21.4 (CH_3). **(ESI) MS** calcd for $C_{30}H_{26}KN_2O_2S$ $[M+K]^+$ 517.13, found 517.18.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-4-methyl-*N*-[3-(thiophen-2-yl)prop-2-yn-1-yl]benzenesulfonamide (1l):** The representive procedure **A** was followed using *N*-[2-(1*H*-Indol-3-yl)ethyl]-4-methylbenzenesulfonamide (314 mg, 1.0 mmol) and 2-(3-bromoprop-1-yn-1-yl)thiophene (300 mg, 1.5 mmol). Purification by chromatography on silica gel yielded **1l** (302 mg, 74%) as a yellow solid. M. p. = 95.6 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (bs, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.29-7.19 (m, 4H), 7.15-7.09 (m, 2H), 6.98 (d, *J* = 3.5 Hz, 1H), 6.94 (dd, *J* = 5.2, 3.5 Hz, 1H), 4.43 (s, 2H), 3.62-3.57 (m, 2H), 3.18-3.12 (m, 2H), 2.42 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5 (C_q), 136.3 (C_q), 135.8 (C_q), 132.3 (2 CH), 129.6 (CH), 127.7 (CH), 127.3 (C_q), 126.8 (2 CH), 122.3 (C_q), 122.1 (CH), 119.5 (CH), 118.7 (CH), 112.3 (C_q), 111.2 (CH), 86.0 (C_q), 79.0 (C_q), 47.2 (CH_2), 37.8 (CH_2), 24.4 (CH_2), 21.5 (CH_3). **(ESI) MS** calcd for $C_{24}H_{22}KN_2O_2S_2$ $[M+K]^+$ 473.07 found 473.08.

***N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-(but-2-yn-1-yl)methanesulfonamide (3a):** The representative procedure **A** was followed using *N*-[2-(1*H*-indol-3-yl)ethyl]methanesulfonamide (180 mg, 0.76 mmol) and 1-bromo-2-butyne (120 mg, 0.90 mmol). Purification by chromatography on silica gel yielded **3a** (129 mg, 58 %) as a white solid. M. p. = 94.3 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02

(brs, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.24–7.18 (m, 1H), 7.16–7.07 (m, 2H), 4.08 (d, *J* = 2.4 Hz, 2H), 3.58 (dd, *J* = 8.9, 6.5 Hz, 2H), 3.10 (dd, *J* = 8.8, 6.6 Hz, 2H), 2.88 (s, 3H), 1.84 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.2 (C_q), 127.3 (C_q), 122.2 (2 CH), 119.5 (CH), 118.6 (CH), 112.4 (C_q), 111.2 (CH), 82.0 (C_q), 72.6 (C_q), 46.9 (CH_2), 37.7 (CH_3), 37.0 (CH_2), 24.5 (CH_2), 3.4 (CH_3). **(ESI) MS** calcd for $C_{15}H_{18}N_2NaO_2S$ $[M+Na]^+$ 313.10, found 313.15.

***N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-(but-2-yn-1-yl)-4-chlorobenzenesulfonamide (3b):** The representive procedure **A** was followed using *N*-[2-(1*H*-indol-3-yl)ethyl]-4-chlorobenzenesulfonamide (334 mg, 1.0 mmol) and 1-bromobut-2-yne (198 mg, 1.5 mmol). Purification by chromatography on silica gel yielded **3b** (302 mg, 78%) as a white solid. M. p. = 103.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (bs, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.10 (s, 1H), 4.16 (s, 2H), 3.56-3.50 (m, 2H), 3.15-3.07 (m, 2H), 1.62 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.0 (C_q), 137.5 (C_q), 136.2 (C_q), 129.2 (CH), 128.9 (CH), 127.3 (C_q), 122.3 (CH), 122.2 (CH), 119.5 (CH), 118.6 (CH), 112.2 (C_q), 111.3 (CH), 82.0 (C_q), 71.7 (C_q), 47.0 (CH_2), 37.2 (CH_2), 24.2 (CH_2), 3.3 (CH_3). **ESI MS** calcd for $C_{20}H_{20}ClN_2O_2S$ $[M+H]^+$ 387.09 found 387.09.

***N*-(But-2-yn-1-yl)-4-methyl-*N*-[2-(5-methyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (3c):** The representive procedure **A** was followed using 4-Methyl-*N*-[2-(5-methyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (426 mg, 1.3 mmol) and 1-bromobut-2-yne (257 mg, 1.9 mmol). Purification by chromatography on silica gel yielded **3c** (395 mg, 80%) as a white solid. M. p. = 119.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (bs, 1H), 7.79 (d, *J* = 7.9 Hz, 2H),

7.45 (s, 1H), 7.33-7.27 (m, 3H), 7.08-7.04 (m, 2H), 4.22-4.18 (m, 2H), 3.55 (dd, *J* = 9.8, 6.2 Hz, 2H), 3.09 (dd, *J* = 9.8, 6.2 Hz, 2H), 2.51 (s, 3H), 2.46 (s, 3H), 1.65 (t, *J* = 2.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2 (C_q), 136.1 (C_q), 134.7 (C_q), 129.3 (CH), 128.5 (C_q), 127.8 (CH), 127.6 (C_q), 122.6 (CH), 122.5 (CH), 118.3 (CH), 111.7 (C_q), 111.1 (CH), 81.7 (C_q), 72.1 (C_q), 47.1 (CH_2), 37.3 (CH_2), 24.3 (CH_2), 21.6 (CH_3), 21.5 (CH_3), 3.3 (CH_3). **(ESI) MS** calcd for $C_{22}H_{25}N_2O_2S$ $[M+H]^+$ 381.16 found 381.14.

***N*-(But-2-yn-1-yl)-4-methyl-*N*-{2-[5-(*p*-tolyl)-1*H*-indol-3-yl]ethyl}benzenesulfonamide (3d):** The representive procedure **A** was followed using 4-Methyl-*N*-{2-[5-(*p*-tolyl)-1*H*-indol-3-yl]ethyl}benzenesulfonamide (550 mg, 1.4 mmol) and 1-bromobut-2-yne (272 mg, 2.1 mmol). Purification by chromatography on silica gel yielded **3d** (420 mg, 68%) as a viscous yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (bs, 1H), 7.82 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.49-7.41 (m, 2H), 7.32-7.24 (m, 4H), 7.17-7.12 (m, 1H), 4.19-4.15 (m, 2H), 3.59-3.41 (m, 2H), 3.19-2.95 (m, 2H), 2.43 (s, 3H), 2.42 (d, *J* = 8.2 Hz, 3H), 1.68-1.52 (m, 3H). **^{13}C NMR** ($CDCl_3$, 101 MHz,) δ 143.4 (rotB, C_q), 143.2 (rotA, C_q), 139.7 (C_q), 136.0 (C_q), 135.9 (rotB, C_q), 135.7 (rotA, C_q), 134.6 (C_q), 133.0 (C_q), 129.4 (CH), 129.3 (CH), 128.4 (rotB, C_q), 127.8 (rotA, C_q), 127.7 (CH), 127.2 (CH), 123.8 (rotB, CH), 123.0 (rotA, CH), 122.3 (rotB, CH), 121.8 (rotA, CH), 118.2 (rotB, CH), 116.9 (rotA, CH), 112.7 (rotB, C_q), 112.3 (rotA, C_q), 112.1 (rotB, CH), 111.5 (rotA, CH), 82.0 (rotB, C_q), 81.8 (rotA, C_q), 71.9 (rotA, C_q), 71.8 (rotB, C_q), 46.9 (rotA, CH_2), 46.7 (rotB, CH_2), 37.3 (rotA, CH_2), 37.2 (rotB, CH_2), 24.3 (rotA, CH_2), 24.1 (rotB, CH_2), 21.5 (rotB, CH_3), 21.4 (rotA, CH_3), 21.1 (CH_3), 3.3 (rotB, CH_3), 3.2 (rotA, CH_3). **(ESI) MS** calcd for $C_{28}H_{28}N_2NaO_2S$ $[M+Na]^+$ 479.18 found 479.27.

***N*-{2-{5-[(*tert*-butyldimethylsilyl)oxy]-1*H*-indol-3-yl}ethyl}-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (3e):** The representative procedure **A** was followed using *N*-{2-{5-[(*tert*-butyldimethylsilyl)oxy]-1H-indol-3-yl}ethyl}-4-methylbenzenesulfonamide (386 mg, 0.87 mmol) and (3-bromoprop-1-yn-1-yl)benzene (200 mg, 1.02 mmol). Purification by chromatography on silica gel yielded **3e** (200 mg, 41 %) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (brs, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.26–7.20 (m, 6H), 7.09–7.04 (m, 2H), 6.76 (dd, *J* = 8.6, 2.3 Hz, 1H), 4.37 (s, 2H), 3.56 (dd, *J* = 8.9, 6.5 Hz, 2H), 3.07 (dd, *J* = 8.8, 6.6 Hz, 2H), 2.31 (s, 3H), 0.98 (s, 9H), 0.17 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2 (C_q), 143.3 (C_q), 136.0 (C_q), 131.7 (C_q), 131.5 (CH), 129.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (C_q), 127.7 (CH), 123.0 (CH), 122.2 (C_q), 116.4 (CH), 111.9 (C_q), 111.4 (CH), 108.1 (CH), 85.5 (C_q), 82.0 (C_q), 47.0 (CH_2), 37.6 (CH_2), 25.8 (C_q), 24.5 (CH_2), 21.4 (CH_2), 18.2 (CH_3), -4.5 (CH_3). **(ESI) MS** calcd for $C_{32}H_{38}KN_2O_3SSi$ $[M+K]^+$ 597.20, found 597.21.

***N*-(But-2-yn-1-yl)-*N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (3f)**: The representive procedure **A** was followed using *N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (447 mg, 1.3 mmol) and 1-bromobut-2-yne (257 mg, 1.9 mmol). Purification by chromatography on silica gel yielded **3f** (370 mg, 72%) as a white solid. M. p. = 112.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (bs, 1H), 7.75 (dd, *J* = 7.2 Hz, 2H), 7.30-7.25 (m, 3H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.09-7.07 (m, 1H), 6.88 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.14 (q, *J* = 2.4 Hz, 2H), 3.90 (s, 3H), 3.54-3.48 (m, 2H), 3.09-3.05 (m, 2H), 2.42 (s, 3H), 1.60 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.1 (C_q), 143.2 (C_q), 136.2 (C_q), 131.4 (C_q), 129.3 (CH), 127.8 (C_q), 127.7 (CH), 123.0 (CH), 112.3 (CH), 112.2 (CH), 111.9 (C_q), 100.7 (CH), 81.5

(C_q), 72.1 (C_q), 56.0 (CH_3), 46.9 (CH_2), 37.3 (CH_2), 24.5 (CH_2), 21.5 (CH_3), 3.2 (CH_3). **(ESI) MS** calcd for $C_{22}H_{25}N_2O_3S$ $[M+H]^+$ 397.16 found 397.18.

***N*-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (3g):** The representive procedure **A** was followed using *N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (412 mg, 1.2 mmol) and (3-bromoprop-1-yn-1-yl)benzene (347 mg, 1.8 mmol). Purification by chromatography on silica gel yielded **2g** (395 mg, 72%) as a white solid. M. p. = 135.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 8.12 (d, *J* = 8.2 Hz, 2H), 7.32-7.22 (m, 6H), 7.12-7.07 (m, 4H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.42 (s, 2H), 3.77 (m, 3H), 3.63-3.58 (m, 2H), 3.16-3.10 (m, 2H), 2.35 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.1 (C_q), 143.4 (C_q), 135.9 (C_q), 131.5 (CH), 131.3 (C_q), 129.5 (CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.7 (C_q), 123.0 (CH), 122.2 (C_q), 112.5 (CH), 112.1 (C_q), 112.0 (CH), 100.3 (CH), 85.6 (C_q), 82.0 (C_q), 55.8 (CH_3), 47.0 (CH_2), 37.6 (CH_2), 24.6 (CH_2), 21.4 (CH_3). **(ESI) MS** calcd for $C_{27}H_{26}N_2NaO_3S$ $[M+Na]^+$ 481.16 found 481.26.

***N*-(But-2-yn-1-yl)-*N*-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (3h):** The representive procedure **A** was followed using *N*-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (564 mg, 1.7 mmol) and 1-bromobut-2-yne (330 mg, 2.5 mmol). Purification by chromatography on silica gel yielded **3h** (400 mg, 61%) as a yellow solid. M. p. = 123.7 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (bs, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.31-7.24 (m, 4H), 7.12 (s, 1H), 6.94 (t, *J* = 9.6 Hz, 1H), 4.15 (s, 2H), 3.51 (t, *J* = 7.6 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.43 (s, 3H), 1.69 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9 (d, *J* = 240 Hz, C_q), 143.4 (C_q), 135.9 (C_q), 132.8 (C_q), 129.4 (CH), 127.8 (CH), 127.7 (C_q), 124.3 (CH), 112.4 (d, *J* = 6 Hz, C_q), 112.0 (d, *J* = 10 Hz, CH), 110.3 (d, *J* = 26 Hz, CH), 103.5 (d, *J* = 23 Hz, CH),

82.0 (C_q), 71.9 (C_q), 46.7 (CH_2), 37.2 (CH_2), 24.1 (CH_2), 21.5 (CH_3), 3.3 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -124.7 Hz. **(ESI) MS** calcd for $C_{21}H_{21}FN_2NaO_2S$ $[M+Na]^+$ 407.12 found 407.12.

***N*-(but-2-yn-1-yl)-*N*-[2-(5-chloro-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (3i):** The representative procedure **A** was followed using *N*-(2-(5-chloro-1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide (400 mg, 1.14 mmol) and 1-bromo-2-butyne (183 mg, 1.4 mmol). Purification by chromatography on silica gel yielded **3i** (274 mg, 60 %) as a white solid. M. p. = 130.4 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 (brs, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.28 (m, 5H), 7.19 – 6.94 (m, 2H), 4.12 (d, *J* = 2.4 Hz, 2H), 3.17–2.91 (m, 2H), 2.40 (s, 3H), 1.63 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.3 (C_q), 135.9 (C_q), 134.5 (C_q), 129.3 (CH), 128.5 (C_q), 127.7 (CH), 125.1 (C_q), 123.7 (CH), 122.3 (CH), 118.2 (CH), 112.3 (C_q), 112.2 (CH), 82.0 (C_q), 71.8 (C_q), 46.6 (CH_2), 37.2 (CH_2), 24.0 (CH_2), 21.5 (CH_3), 3.3 (CH_3). **(ESI) MS** calcd for $C_{21}H_{22}ClN_2O_2S$ $[M+H]^+$ 401.11, found 401.17.

***N*-[2-(5-chloro-1*H*-indol-3-yl)ethyl]-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (3j):** The representative procedure **A** was followed using *N*-[2-(5-chloro-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (230 mg,0.66 mmol) and (3-bromoprop-1-yn-1-yl)benzene (154 mg, 0.8 mmol). Purification by chromatography on silica gel yielded **3j** (265 mg, 87 %) as a pale-yellow oil. **^{1}H NMR** (400 MHz, $CHCl_3$) δ 8.27 (brs, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.57 (s, 1H), 7.31–7.25 (m, 6H), 7.16–7.12 (m, 4H), 4.41 (s, 2H), 3.59 (dd, *J* = 8.8, 6.5 Hz, 2H), 3.10 (dd, *J* = 8.8, 6.5 Hz, 2H), 2.35 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5 (C_q), 135.7 (C_q), 134.5 (C_q), 131.6 (CH), 129.5 (CH), 128.4 (CH), 128.4 (C_q), 128.1 (CH), 127.7 (CH), 125.2 (C_q), 123.8 (CH), 122.3 (CH), 122.0 (C_q), 118.0 (CH), 112.3 (CH), 112.0 (C_q), 85.8 (C_q), 81.7 (C_q), 46.8

(CH_2), 37.5 (CH_2), 24.1 (CH_2), 21.3 (CH_3). **(ESI) MS** calcd for $C_{26}H_{24}ClN_2O_2S$ $[M+H]^+$ 463.12, found 463.19.

***N*-(But-2-yn-1-yl)-*N*-[2-(6-chloro-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (3k):** The representive procedure **A** was followed using *N*-[2-(6-chloro-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (650 mg, 1.9 mmol) and 1-bromobut-2-yne (376 mg, 2.9 mmol). Purification by chromatography on silica gel yielded **3k** (409 mg, 54%) as a yellow viscous oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (bs, 1H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.30-7.25 (m, 2H), 7.11-7.06 (m, 2H), 4.13-4.11 (m, 2H), 3.52-3.44 (m, 2H), 3.08-3.02 (m, 2H), 2.42 (s, 3H), 1.60 (t, *J* = 1.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 136.6 (C_q), 135.9 (C_q), 129.4 (CH), 127.9 (C_q), 127.8 (CH), 126.0 (C_q), 123.0 (CH), 120.1 (CH), 119.5 (CH), 112.6 (C_q), 111.2 (CH), 81.7 (C_q), 71.9 (C_q), 46.8 (CH_2), 37.3 (CH_2), 24.2 (CH_2), 21.5 (CH_3), 3.3 (CH_3). **(ESI) MS** calcd for $C_{21}H_{21}ClN_2NaO_2S$ $[M+Na]^+$ 423.09 found 423.18.

***N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-*N*-(3-(4'-(3-((N-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-4-methylphenyl)sulfonamido)prop-1-yn-1-yl)-[1,1'-biphenyl]-4-yl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (5a):** The representive procedure **A** was followed using *N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (430 mg, 2.5 mmol) and 4,4'-bis(3-bromoprop-1-yn-1-yl)-1,1'-biphenyl (195 mg, 0.5 mmol). Purification by chromatography on silica gel yielded **5a** (249 mg, 55%) as a yellow solid. M. p. = 202.8 °C. **^{1}H NMR** (400 MHz, d_6-DMSO) δ 10.70 (bs, 1H x2), 7.69 (d, *J* = 8.2 Hz, 2H x2), 7.53 (d, *J* = 8.2 Hz, 2H x2), 7.32-7.28 (m, 2H x2), 7.25 (d, *J* = 8.8 Hz, 1H x2), 7.16 (d, *J* = 2.1 Hz, 1H x2), 7.10 (d, *J* =8.2 Hz, 2H x2), 6.98 (d, *J* = 2.1 Hz, 1H x2), 6.71 (dd, *J* = 8.8, 2.1 Hz, 1H x2), 4.42 (s, 2H x2), 3.61 (s, 3H

x2), 3.47-3.41 (m, 2H x2), 3.03-2.95 (m, 2H x2), 2.22 (s, 3H x2). **^{13}C NMR** (101 MHz, *d*$_6$-DMSO) δ 153.5 (C_q), 144.0 (C_q), 139.5 (C_q), 136.7 (C_q), 132.3 (CH), 131.9 (C_q), 130.1 (CH), 127.8 (C_q), 127.7 (CH), 126.9 (CH), 124.2 (CH) , 121.4 (C_q), 112.7 (C_q), 111.6 (CH), 110.8 (CH), 100.4 (CH), 85.2 (C_q), 84.1 (C_q), 55.6 (CH_3), 47.4 (CH_2), 37.5 (CH_2), 24.3 (CH_2), 21.3 (CH_3). **(ESI) MS** calcd for $C_{54}H_{50}KN_4O_6S_2$ $[M+Na]^+$ 953.28 found 953.29.

***N*-(But-2-yn-1-yl)-4-methyl-*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (7b):** The representive procedure **A** was followed using 4-Methyl-*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (328 mg, 1.0 mmol) and 1-bromobut-2-yne (196 mg, 1.5 mmol). Purification by chromatography on silica gel yielded **7b** (300 mg, 79%) as a white solid. M. p. = 100.5 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.35-7.22 (m, 4H), 7.18-7.11 (m, 1H), 6.97 (s, 1H), 4.16 (d, *J* = 2.4 Hz, 2H), 3.77 (s, 3H), 3.54-3.46 (m, 2H), 3.12-3.06 (m, 2H), 2.43 (s, 3H), 2.61 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2 (C_q), 136.9 (C_q), 136.0 (C_q), 129.3 (CH), 127.8 (CH), 127.7 (C_q), 127.0 (CH), 121.6 (CH), 118.9 (CH), 118.8 (CH), 110.9 (C_q), 109.3 (CH), 81.6 (C_q), 72.0 (C_q), 47.1 (CH_2), 37.2 (CH_2), 32.7 (CH_3), 24.2 (CH_2), 21.5 (CH_3), 3.3 (CH_3). **(ESI) MS** calcd for $C_{22}H_{25}N_2O_2S$ $[M+H]^+$ 381.16 found 381.18.

4-Methyl-*N*-[2-(2-methyl-1*H*-indol-3-yl)ethyl]-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (7c): The representive procedure **A** was followed using 4-Methyl-*N*-[2-(2-methyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (328 mg, 1.0 mmol) and (3-bromoprop-1-yn-1-yl)benzene (289 mg, 1.5 mmol). Purification by chromatography on silica gel yielded **3o** (298 mg, 68%) as a yellow solid. M. p. = 77.6 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (bs, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.33-7.23 (m, 6H), 7.14-7.11 (m,

3H), 7.03 (t, *J* = 7.8 Hz, 1H), 4.45 (s, 2H), 3.52-3.45 (m, 2H), 3.13-3.07 (m, 2H), 2.41 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4 (C_q), 136.9 (C_q), 136.2 (C_q), 132.0 (C_q), 131.6 (CH), 129.5 (CH), 128.5 (CH), 128.4 (C_q), 128.2 (CH), 127.7 (CH), 122.2 (C_q), 121.1 (CH), 119.4 (CH), 117.9 (CH), 110.3 (CH), 107.9 (C_q), 85.7 (C_q), 82.1 (C_q), 47.1 (CH_2), 37.9 (CH_2), 23.7 (CH_2), 21.4 (CH_3), 11.6 (CH_3). **(ESI) MS** calcd for $C_{27}H_{26}KN_2O_2S$ $[M+K]^+$ 481.13 found 481.15.

(*E*)-1-(Prop-1-en-1-yl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2a): The representive procedure **B** was followed using **1a** (73.2 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.78) yielded **2a** (57.2 mg, 78%) as a white solid. M. p. = 80.5 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (bs, 1H), 7.70-7-68 (m, 2H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.33-7.31 (m, 1H), 7.21-7.16 (m, 3H), 7.10 (ddd, *J* = 7.6, 6.8, 1.1 Hz, 1H), 5.72-5.64 (m, 1H), 5.64-5.53 (m, 2H), 4.09 (dt, *J* = 13.8, 3.4 Hz, 1H), 3.32 (dt, *J* = 13.8, 7.8 Hz, 1H), 2.65 (dd, *J* = 7.8, 3.4 Hz, 2H), 2.36 (s, 3H), 1.68 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2 (C_q), 138.1 (C_q), 136.0 (C_q), 131.1 (C_q), 130.1 (CH), 129.4 (CH), 128.4 (CH), 127.1 (CH), 126.8 (C_q), 122.1 (CH), 119.6 (CH), 118.3 (CH), 110.9 (CH), 108.7 (C_q), 54.6 (CH), 39.9 (CH_2), 21.4 (CH_3), 20.9 (CH_2), 17.6 (CH_3). **(ESI) MS** calcd for $C_{21}H_{22}N_2NaO_2S$ $[M+Na]^+$ 389.13 found 389.15.

(*E*)-1-(But-1-en-1-yl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2b): The representive procedure **B** was followed using **1b** (76.0 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.70) yielded **2b** (41.4 mg, 54%) as a yellow solid. M. p. = 72.3 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (bs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.34-7.30 (m, 1H), 7.21-7.14 (m, 3H), 7.10 (ddd, *J* = 7.6, 6.8, 1.1 Hz, 1H), 5.75-5.68 (m, 1H), 5.64-5.51 (m, 2H), 4.10 (dt, *J* = 13.5, 3.5 Hz, 1H), 3.32 (dt, *J* =

13.5, 7.9 Hz, 1H), 2.66 (dd, *J* = 7.9, 3.5 Hz, 2H), 2.36 (s, 3H), 2.08-1.98 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1 (C_q), 138.2 (C_q), 136.8 (CH), 136.0 (C_q), 131.1 (C_q), 129.4 (CH), 127.1 (CH), 126.8 (C_q), 126.0 (CH), 122.1 (CH), 119.5 (CH), 118.2 (CH), 110.9 (CH), 108.8 (C_q), 54.6 (CH), 39.8 (CH_2), 25.0 (CH_2), 21.4 (CH_3), 21.0 (CH_2), 13.0 (CH_3). **(ESI) MS** calcd for $C_{22}H_{25}N_2O_2S$ $[M+H]^+$ 381.16 found 381.18.

(*E*)-1-Styryl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2c): The representive procedure **B** was followed using **1c** (61.6 mg, 0.14 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.67) yielded **2c** (50.8 mg, 85%) as a yellow solid. M. p. = 167.6 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.53-7-50 (m, 1H), 7.46-7.41 (m, 1H), 7.39-7.24 (m, 5H), 7.22-7.18 (m, 1H), 7.15-7.11 (m, 3H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.25 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.83 (d, *J* = 5.8 Hz, 1H), 4.15 (dt, *J* = 13.5, 3.4 Hz, 1H), 3.38 (dt, *J* = 13.5, 8.0 Hz, 1H), 2.70 (dd, *J* = 8.0, 3.4 Hz, 2H), 2.31 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 137.9 (C_q), 136.2 (C_q), 135.8 (C_q), 133.5 (C_q), 130.2 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.1 (CH), 126.8 (C_q), 126.2 (CH), 122.3 (CH), 119.6 (CH), 118.3 (CH), 111.1 (CH), 109.1 (C_q), 54.8 (CH), 40.1 (CH_2), 21.4 (CH_3), 21.0 (CH_2). **(ESI) MS** calcd for $C_{26}H_{25}N_2O_2S$ $[M+H]^+$ 429.16 found 429.19.

(*E*)-1-(2-fluorostyryl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2d): The representative procedure **B** was followed using **1d** (89.3 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexane/EtOAc 8:2 = 0.24) yielded **2d** (75 mg, 84 %) as a white solid. M. p. = 172.3 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (brs, 1H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.25–7.03 (m, 8H), 6.70 (d, *J* = 16.0 Hz, 1H), 6.32 (dd, *J* = 16.0, 7.1 Hz, 1H), 5.82 (d, *J* = 7.0 Hz, 1H), 4.17 (d, *J* = 13.7 Hz, 1H), 3.43–

3.36 (m, 1H), 2.72 (d, *J* = 4.8 Hz, 2H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2 (d, *J* = 250.1 Hz, C_q), 143.2 (C_q), 137.6 (C_q), 136.2 (C_q), 130.1 (C_q), 129.4 (CH), 129.4 (d, *J* = 7.7 Hz, CH), 128.7 (d, *J* = 5.3 Hz, CH), 127.8 (d, *J* = 3.3 Hz, CH), 127.0 (CH), 126.6 (C_q), 125.8 (d, *J* = 3.3 Hz, CH), 124.0 (d, *J* = 3.6 Hz, CH), 123.6 (d, *J* = 12.0 Hz, CH), 122.2 (CH), 119.5 (CH), 118.2 (CH), 115.7 (d, *J* = 22.0 Hz, C_q), 111.1 (CH), 108.9 (C_q), 55.0 (CH), 40.2 (CH_2), 21.3 (CH_3), 20.9 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.9 Hz. **(ESI) MS** calcd for $C_{26}H_{24}FN_2O_2F$ $[M+H]^+$ 447.15, found 447.19.

(*E*)-1-(3-Fluorostyryl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2e): The representive procedure **B** was followed using **1e** (89.2 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.69) yielded **2e** (78.4 mg, 88%) as a yellow solid. M. p. = 163.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.97 (bs, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.48-7.44 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.29-7.19 (m, 3H), 7.15-7.10 (m, 3H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.97-6.88 (m, 1H), 6.47 (d, *J* = 15.3 Hz, 1H), 6.23 (dd, *J* = 15.3, 6.5 Hz, 1H), 5.82 (d, *J* = 6.5 Hz, 1H), 4.20-4.13 (m, 1H), 3.44-3.30 (m, 1H), 2.75-2.68 (m, 2H), 2.32 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (d, *J* = 245 Hz, C_q), 143.4 (C_q), 138.1 (d, *J* = 8 Hz, C_q), 137.9 (C_q), 136.2 (C_q), 132.3 (C_q), 130.2 (d, *J* = 5 Hz, CH), 129.6 (CH), 128.5 (CH), 127.6 (C_q), 127.0 (CH), 126.7 (CH), 122.7 (d, *J* = 3 Hz, CH), 122.4 (CH), 119.7 (CH), 118.4 (CH), 114.9 (d, *J* = 20 Hz, CH), 113.1 (d, *J* = 25 Hz, CH), 111.1 (CH), 109.2 (C_q), 54.6 (CH), 40.1 (CH_2), 21.4 (CH_3), 21.0 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.0 Hz. **(ESI) MS** calcd for $C_{26}H_{24}FN_2O_2S$ $[M+H]^+$ 447.15 found 447.22.

(*E*)-1-(3-methylstyryl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2f): The representative procedure **B** was followed using **1f** (88.5 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexane/EtOAc 8:2 =

0.34) yielded **2f** (44.3 mg, 50 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (brs, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.20–7.02 (m, 8H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.23 (dd, *J* = 15.8, 6.6 Hz, 1H), 5.80 (d, *J* = 6.6 Hz, 1H), 4.16–4.09 (m, 1H), 3.42–3.32 (m, 1H), 2.70-2.66 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.2 (C_q), 138.1 (C_q), 137.9 (C_q), 136.1 (C_q), 135.7 (C_q), 133.5 (CH), 130.4 (C_q), 129.5 (CH), 128.9 (CH), 128.4 (CH), 127.4 (CH), 127.0 (CH), 126.7 (C_q), 126.0 (CH), 123.9 (CH), 122.2 (CH), 119.5 (CH), 118.2 (CH), 111.0 (CH), 109.0 (C_q), 54.7 (CH), 40.0 (CH_2), 21.3 (CH_3), 21.2 (CH_3), 20.9 (CH_2). **(ESI) MS** calcd for $C_{27}H_{27}N_2O_2S$ $[M+H]^+$ 443.18, found 443.16.

(*E*)-1-(3-Fluoro-4-methylstyryl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2g): The representive procedure **B** was followed using **1g** (92.0 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.81) yielded **2g** (59.4 mg, 65%) as a yellow solid. M. p. = 177.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (bs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.22-7.17 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.12-7.06 (m, 2H), 6.90 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.85 (dd, *J* = 10.2, 1.2 Hz, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.82 (d, *J* = 5.8 Hz, 1H), 4.20-4.12 (m, 1H), 3.42-3.32 (m, 1H), 2.72-2.66 (m, 2H), 2.32 (s, 3H), 2.27 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.3 (d, *J* = 248 Hz, C_q), 143.4 (C_q), 137.8 (C_q), 136.2 (C_q), 135.6 (d, *J* = 8 Hz, C_q), 132.3 (d, *J* = 2 Hz, CH), 131.5 (d, *J* = 5 Hz, CH), 130.2 (CH), 129.6 (CH), 127.1 (CH), 126.7 (C_q), 126.5 (CH), 124.8 (d, *J* = 17 Hz, C_q), 122.5 (d, *J* = 3 Hz, CH), 122.3 (CH), 119.6 (CH), 118.4 (CH), 112.7 (d, *J* = 23 Hz, C_q), 111.1 (CH), 109.1 (C_q), 54.6 (CH), 40.1 (CH_2), 21.4 (CH_3), 21.0 (CH_2), 14.4 (d, *J* = 3 Hz, CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.5 Hz. **(ESI) MS** calcd for $C_{27}H_{26}FN_2O_2S$ $[M+H]^+$ 461.17 found 461.20.

(*E*)-1-(4-methoxystyryl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2h): The representative procedure **B** was followed using **1h** (91.7 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexane/EtOAc 8:2 = 0.24) yielded **2h** (58.7 mg, 64 %) as a white solid. M. p. = 185.3 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 (brs, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.34–7.28 (m, 2H), 7.21–7.11 (m, 4H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.10 (dd, *J* = 15.8, 6.9 Hz, 1H), 5.79 (d, *J* = 6.9 Hz, 1H), 4.16–4.11 (m, 1H), 3.82 (s, 3H), 3.42–3.33 (m, 1H), 2.72–2.68 (m, 2H), 2.32 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.7 (C_q), 143.1 (C_q), 138.0 (C_q), 136.1 (C_q), 133.0 (CH), 130.6 (C_q), 129.5 (CH), 128.5 (C_q), 128.0 (CH), 127.1 (CH), 126.7 (C_q), 123.9 (CH), 122.2 (CH), 119.6 (CH), 118.3 (CH), 114.0 (CH), 111.0 (CH), 109.1 (C_q), 55.3 (CH), 54.8 (CH_3), 40.0 (CH_2), 21.4 (CH_3), 21.0 (CH_2). **(ESI) MS** calcd for $C_{27}H_{27}N_2O_3S$ $[M+H]^+$ 459.17, found 459.19.

(*E*)-2-Tosyl-1-[4-(trifluoromethyl)styryl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2i): The representive procedure **B** was followed using **1i** (99.2 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f n-hexanes/EtOAc 6:4 = 0.67) yielded **2i** (68.3 mg, 69%) as a yellow solid. M. p. = 220.5 °C. **^{1}H NMR** (400 MHz, d_6-DMSO) δ 10.92 (bs, 1H), 7.72-7.64 (m, 5H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 6.50 (dd, *J* = 15.8, 6.9 Hz, 1H), 5.71 (d, *J* = 6.9 Hz, 1H), 4.17-4.09 (m, 1H), 3.49-3.38 (m, 1H), 2.73-2.65 (m, 1H), 2.63-2.55 (m, 1H), 2.22 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO) δ 143.5 (C_q), 140.6 (C_q), 138.0 (C_q), 136.6 (C_q), 133.3 (C_q), 131.4 (CH), 130.8 (CH), 130.0 (CH), 128.4 (d, *J* = 33 Hz, C_q), 127.7 (CH), 127.3 (CH), 126.6 (C_q), 125.8 (d, *J* = 4Hz, CH), 124.4 (d, *J* = 272 Hz, C_q), 121.9 (CH), 119.1 (CH), 118.4 (CH), 111.7 (CH), 107.3 (C_q), 55.0 (CH), 39.8 (CH_2),

21.3 (CH_3), 21.0 (CH_2). **^{19}F NMR** (376 MHz, d_6-DMSO) δ -61.0 Hz. **(ESI) MS** calcd for $C_{27}H_{24}F_3N_2O_2S$ $[M+H]^+$ 497.15 found 497.23.

(*E*)-1-{2-[(1,1'-Biphenyl)-4-yl]vinyl}-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2j): The representive procedure **B** was followed using **1j** (100.8 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.78) yielded **2j** (73.7 mg, 73%) as a yellow solid. M. p. = 124.5 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (bs, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.51-7.44 (m, 3H), 7.43-7.38 (m, 1H), 7.37-7.30 (m, 3H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.17-7.10 (m, 3H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.31 (dd, *J* = 15.9, 6.7 Hz, 1H), 5.89 (d, *J* = 6.7 Hz, 1H), 4.18 (td, *J* = 13.7, 3.5 Hz, 1H), 3.42 (td, *J* = 13.7, 8.2 Hz, 1H), 2.73 (dd, *J* = 8.2, 3.8 Hz, 2H), 2.31 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 140.9 (C_q), 140.4 (C_q), 137.9 (C_q), 136.2 (C_q), 134.9 (C_q), 133.0 (CH), 130.4 (C_q), 129.6 (CH), 128.9 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 126.7 (C_q), 126.3 (CH), 122.3 (CH), 119.6 (CH), 118.3 (CH), 111.2 (CH), 109.0 (C_q), 54.8 (CH), 40.1 (CH_2), 21.4 (CH_3), 21.0 (CH_2). **(ESI) MS** calcd for $C_{32}H_{29}N_2O_2S$ $[M+H]^+$ 505.19 found 505.23.

(*E*)-1-(2-(naphthalen-2-yl)vinyl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2k): The representative procedure **B** was followed using **1k** (95.7 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexane/EtOAc 8:2 = 0.24) yielded **2k** (47.8 mg, 50 %) as a white solid. M. p. = 161.6 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (brs, 1H), 7.80–7.63 (m, 6H), 7.47–7.40 (m, 4H), 7.33–7.31 (m, 1H), 7.20-7.17 (m, 1H), 7.13–7.09 (m, 3H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.34 (dd, *J* = 15.8, 6.9 Hz, 1H), 5.84 (d, *J* = 6.9 Hz, 1H), 4.15 (d, *J* = 13.1 Hz, 1H), 3.39 (dt, *J* = 14.7, 7.9 Hz, 1H), 2.72–2.69 (m, 2H), 2.27 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2 (C_q), 137.9 (C_q), 136.1 (C_q), 133.6 (C_q),

133.4 (CH), 133.2 (C_q), 130.3 (C_q), 129.5 (CH), 128.5 (C_q), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.1 (CH), 127.1 (CH), 126.7 (C_q), 126.4 (CH), 126.4 (CH), 126.2 (CH), 123.4 (CH), 122.3 (CH), 119.7 (CH), 118.4 (CH), 111.0 (CH), 109.3 (C_q), 54.8 (CH), 40.1 (CH_2), 21.4 (CH_3), 21.0 (CH_2). **(ESI) MS** calcd for $C_{30}H_{27}N_2O_2S$ $[M+H]^+$ 479.18, found 479.32.

(*E*)-1-[2-(Thiophen-2-yl)vinyl]-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2l): The representive procedure **B** was followed using **1l** (82.0 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.64) yielded **2l** (61.6 mg, 71%) as a yellow solid. M. p. = 172.0 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.22-7.11 (m, 5H), 6.96 (dd, *J* = 5.6, 3.4 Hz, 1H), 6.91 (d, *J* = 3.4 Hz, 1H), 6.62 (d, *J* = 15.8, 1H), 6.09 (dd, *J* = 15.8, 6.7 Hz, 1H), 5.80 (d, *J* = 6.7 Hz, 1H), 4.16-4.13 (m, 1H), 3.41-3.33 (m, 1H), 2.70-2.68 (m, 2H). 2.32 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 140.9 (C_q), 137.9 (C_q), 136.2 (C_q), 130.2 (C_q), 129.6 (CH), 127.5 (C_q), 127.0 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 125.6 (CH), 125.2 (CH), 122.3 (CH), 119.7 (CH), 118.3 (CH), 111.1 (CH), 109.2 (C_q), 54.5 (CH), 40.0 (CH_2), 21.4 (CH_3), 20.9 (CH_2). **(ESI) MS** calcd for $C_{24}H_{23}N_2O_2S_2$ $[M+H]^+$ 435.12 found 435.18.

(*E*)-2-(methylsulfonyl)-1-(prop-1-en-1-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4a): The representative procedure **B** was followed using **3a** (58.1 mg, 0.2 mmol). Purification by chromatography on silica gel (R_f *n*-hexane/EtOAc 8:2 = 0.17) yielded **4a** (40.1 mg, 69 %) as a white solid. M. p. = 177.3 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (brs, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.22–7.11 (m, 2H), 5.74–5.71 (m, 2H), 5.44 (d, *J* = 5.0 Hz, 1H), 4.10 (dd, *J* = 13.8, 5.6 Hz, 1H), 3.36 (ddd, *J* = 13.6, 11.8, 4.4 Hz, 1H), 2.95 (ddd, *J* = 17.1, 11.8, 5.8 Hz, 1H), 2.87–2.77 (m, 1H), 2.83 (s, 3H), 1.74 (d,

J = 4.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.1 (C_q), 131.0 (C_q), 130.8 (CH), 127.9 (CH), 126.7 (C_q), 122.3 (CH), 119.7 (CH), 118.3 (CH), 111.0 (CH), 108.5 (C_q), 54.4 (CH), 40.1 (CH_2), 39.6 (CH_2), 21.2 (CH_3), 17.6 (CH_3). **(ESI) MS** calcd for $C_{15}H_{19}N_2O_2S$ $[M+H]^+$ 291.12, found 291.21.

(*E*)-2-[(4-Chlorophenyl)sulfonyl]-1-(prop-1-en-1-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4b): The representive procedure **B** was followed using **3b** (77.2 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.81) yielded **4b** (52.8 mg, 68%) as a white solid. M. p. = 164.9 °C. **^{1}H NMR** (400 MHz, d_6-acetone) δ 9.93 (bs, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.09 (dt, *J* = 7.8, 1.2 Hz, 1H), 6.99 (dt, *J* = 7.8, 1.2 Hz, 1H), 5.74-5.53 (m, 3H), 4.19-4.12 (m, 1H), 3.43-3.33 (m, 1H), 2.73-2.58 (m, 2H), 1.63 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 138.0 (C_q), 136.6 (C_q), 131.6 (C_q), 129.4 (CH), 129.0 (CH), 128.8 (CH), 128.1 (CH), 126.7 (C_q), 121.5 (CH), 118.9 (CH), 117.9 (CH), 111.0 (CH), 107.3 (C_q), 54.9 (CH), 39.9 (CH_2), 20.7 (CH_2), 16.8 (CH_3). **(ESI) MS** calcd for $C_{20}H_{20}ClN_2O_2S$ $[M+H]^+$ 387.09 found 387.11.

(*E*)-6-Methyl-1-(prop-1-en-1-yl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4c): The representive procedure **B** was followed using **3c** (76.0 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.76) yielded **4c** (47.6 mg, 63%) as a yellow solid. M. p. = 86.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (bs, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.22-7.18 (m, 4H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.70-5-60 (m, 1H), 5.60-5-56 (m, 2H), 4.09 (dt, *J* = 13.9, 3.2 Hz, 1H), 3.32 (dt, *J* = 13.9, 8.2 Hz, 1H), 2.62 (dd, *J* = 8.2, 3.2 Hz, 2H), 2.45 (s, 3H), 2.37 (s, 3H), 1.67 (d, *J* = 5.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1 (C_q), 138.2 (C_q), 134.4 (C_q), 131.2 (C_q), 130.2 (C_q), 130.0 (CH),

129.4 (CH), 128.8 (C_q), 128.5 (CH), 127.1 (CH), 123.6 (CH), 118.0 (CH), 110.6 (CH), 108.2 (C_q), 54.6 (CH), 39.9 (CH_2), 21.4 (CH_2), 21.4 (CH_3), 20.9 (CH_2), 17.5 (CH_3). **(ESI) MS** calcd for $C_{22}H_{25}N_2O_2S$ $[M+H]^+$ 381.16 found 381.20.

(*E*)-1-(Prop-1-en-1-yl)-6-(*p*-tolyl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4d): The representive procedure **B** was followed using **3d** (136.8 mg, 0.30 mmol). Purification by chromatography on silica gel (Rf n-hexanes/EtOAc 6:4 = 0.61) yielded **4d** (84.7 mg, 62%) as a yellow solid. M. p. = 86.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (bs, 1H), 7.73-7.66 (m, 2H), 7.59 (s, 1H), 7.57-7.50 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.33-7.15 (m, 2H), 5.73-5.54 (m, 3H), 4.17-4-04 (m, 1H), 3.39-3.26 (m, 1H), 2.72-2.56 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 1.68 (d, *J* = 5.4 Hz, 3H**). ^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (rotB, C_q), 143.2 (rotA, C_q), 139.6 (C_q), 138.0 (rotA, C_q), 137.9 (rotB, C_q), 136.4 (C_q), 135.4 (rotA, C_q), 134.8 (rotB, C_q), 132.7 (C_q), 130.4 (rotA, C_q), 130.3 (CH), 130.2 (rotB, C_q), 129.5 (CH), 129.4 (CH), 128.3 (CH), 128.0 (rotA, C_q), 127.8 (rotB, C_q), 127.2 (CH), 127.1 (CH), 122.3 (rotB, CH), 121.8 (rotA, CH), 117.6 (rotB, CH), 116.5 (rotA, CH), 112.0 (rotB, CH), 111.1 (rotA, CH), 109.0 (rotA, C_q), 108.4 (rotB, C_q), 54.6 (rotA, CH), 54.5 (rotB, CH), 39.8 (rotA, CH_2), 39.6 (rotB, CH_2), 21.5 (CH_3), 21.0 (CH_2), 20.9 (rotA, CH_3), 20.7 (rotB, CH_3), 17.6 (CH_3). **(ESI) MS** calcd for $C_{28}H_{28}N_2NaO_2S$ $[M+Na]^+$ 479.18 found 479.20.

(*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-styryl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4e): The representative procedure **B** was followed using **4e** (112 mg, 0.2 mmol). Purification by chromatography on silica gel (R.f. *n*-hexane/EtOAc 8:2 = 0.27) yielded **1e** (66 mg, 59 %) as a yellow-pale solid. M. p. = 164.7 °C. **^{1}H NMR** (400 MHz, d_6-acetone) δ 9.87 (brs, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.18 (m, 8H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.68 (dd, *J* = 8.6, 2.4 Hz,

1H), 6.59 (d, *J* = 15.9 Hz, 1H), 6.32 (dd, *J* = 15.8, 7.0 Hz, 1H), 5.80 (d, *J* = 7.0 Hz, 1H), 4.20-4.14 (m, 1H), 3.47–3.40 (m, 1H), 2.65 (dd, *J* = 6.3, 3.0 Hz, 2H), 2.26 (s, 3H), 1.01 (s, 9H), 0.19 (s, 6H). **^{13}C NMR** (101 MHz, *d*$_6$-acetone) δ 149.7 (C_q), 143.9 (C_q), 139.4 (C_q), 137.3 (C_q), 133.4 (CH), 133.2 (C_q), 133.1 (C_q), 130.2 (CH), 129.3 (CH), 128.7 (CH), 128.4 (C_q), 127.9 (CH), 127.5 (CH), 127.1 (CH), 116.3 (CH), 112.3 (CH), 108.5 (CH), 108.2 (C_q), 56.0 (CH_2), 41.0 (CH), 26.2 (^{t}Bu), 21.7 (CH_3), 21.3 (CH_2), 18.8 (C_q), -4.2 (CH_3). **(ESI) MS** calcd for $C_{39}H_{39}N_2O_3SSi$ $[M+H]^+$ 559.24, found 559.27.

(*E*)-6-Methoxy-1-(prop-1-en-1-yl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4f): The representive procedure **B** was followed using **3f** (79.2 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.69) yielded **4f** (45.5 mg, 57%) as a yellow solid. M. p. = 77.5 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (bs, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.21-7.18 (m, 3H), 6.85-6.81 (m, 2H), 5.66-5.54 (m, 3H), 4.12-4.06 (m, 1H), 3.85 (s, 3H), 3.36-3.26 (m, 1H), 2.64-2.59 (m, 2H), 2.36 (s, 3H), 1.66 (d, *J* = 5.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.1 (C_q), 143.1 (C_q), 138.1 (C_q), 132.0 (C_q), 131.1 (C_q), 130.1 (CH), 129.4 (CH), 128.3 (C_q), 127.1 (CH), 127.0 (CH), 111.9 (CH), 111.6 (CH), 106.4 (C_q), 100.5 (CH), 55.9 (CH_3), 54.7 (CH), 39.9 (CH_2), 21.5 (CH_3), 21.0 (CH_2), 17.6 (CH_3). **(ESI) MS** calcd for $C_{22}H_{25}N_2O_3S$ $[M+H]^+$ 397.16 found 397.21.

(*E*)-6-Methoxy-1-styryl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4g): The representive procedure **B** was followed using **3g** (91.6 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.71) yielded **4g** (84.9 mg, 93%) as a yellow solid. M. p. = 185.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (bs, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.32-7.20 (m, 6H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.89 (s, 1H), 6.84 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.48 (d, *J* = 16.6

Hz, 1H), 6.22 (dd, *J* = 16.6, 7.2 Hz, 1H), 5.81 (d, *J* = 7.2 Hz, 1H), 4.18-4.10 (m, 1H), 3.87 (s, 3H), 3.42-3.32 (m, 1H), 2.71-2.60 (m, 2H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.1 (C_q), 143.3 (C_q), 137.8 (C_q), 135.9 (C_q), 133.3 (CH), 131.3 (C_q), 131.2 (C_q), 129.5 (CH), 128.6 (CH), 128.2 (CH), 127.1 (CH), 126.8 (CH), 126.2 (C_q), 112.0 (CH), 111.9 (CH), 108.7 (C_q), 100.5 (CH), 55.9 (CH_3), 54.9 (CH), 40.1 (CH_2), 31.0 (CH_2), 29.3 (CH_2), 21.4 (CH_3). **(ESI) MS** calcd for $C_{27}H_{27}N_2O_3S$ $[M+H]^+$ 459.17 found 459.24.

(*E*)-6-Fluoro-1-(prop-1-en-1-yl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4h): The representive procedure **B** was followed using **3h** (76.8 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.56) yielded **4h** (53.6 mg, 70%) as a yellow solid. M. p. = 106.7 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (bs, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.23-7.16 (m, 3H), 7.03 (dd, *J* = 9.8, 2.2 Hz, 1H), 6.89 (td, *J* = 9.8, 2.2 Hz, 1H), 5.70-5.59 (m, 2H), 5.58-5.50 (m, 1H), 4.11-4.04 (m, 1H), 3.35-3.26 (m, 1H), 2.61-2.54 (m, 2H), 2.37 (s, 3H), 1.65 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.8 (d, *J* = 237 Hz, C_q), 143.3 (C_q), 137.8 (C_q), 133.1 (C_q), 132.5 (C_q), 130.3 (CH), 129.5 (CH), 128.0 (CH), 127.1 (CH), 127.0 (d, *J* = 9Hz, C_q), 111.6 (d, *J* = 10 Hz, CH), 110.1, (d, *J* = 25 Hz, CH), 108.6 (d, *J* = 5 Hz, C_q), 103.3 (d, *J* = 23 Hz, CH), 54.6 (CH), 39.8 (CH_2), 21.5 (CH_3), 20.9 (CH_2), 17.6 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -124.6 Hz. **(ESI) MS** calcd for $C_{21}H_{22}FN_2O_2S$ $[M+H]^+$ 385.13 found 385.11.

(*E*)-6-chloro-1-(prop-1-en-1-yl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4i): The representative procedure **B** was followed using **3i** (80.2 mg, 0.2 mmol). Purification by chromatography on silica gel (R.f. *n*-hexane/EtOAc 8:2 = 0.24) yielded **4i** (47.3 mg, 59 %) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (brs, 1H), 7.65 (d, *J* = 7.9 Hz, 2H), 7.32 (s, 1H), 7.21–7.15 (m,

3H), 7.09–7.06 (m, 1H), 5.65–5.51 (m, 3H), 4.07–4.02 (m, 1H), 3.31–3.24 (m, 1H), 2.58–2.54 (m, 2H), 2.34 (s, 3H), 1.63 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 137.9 (C_q), 134.4 (C_q), 132.7 (C_q), 130.4 (CH), 129.5 (CH), 128.1 (CH), 127.8 (C_q), 127.0 (CH), 125.2 (C_q), 122.3 (CH), 117.8 (CH), 111.9 (CH), 108.4 (C_q), 54.5 (CH), 39.7 (CH_2), 21.4 (CH_3), 20.8 (CH_2), 17.6 (CH_3). **(ESI) MS** calcd for $C_{21}H_{22}ClN_2O_2S$ $[M+H]^+$ 401.11, found 401.13.

(*E*)-6-chloro-1-styryl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4j): The representative procedure **B** was followed using **3j** (92.5 mg, 0.20 mmol). Purification by chromatography on silica gel (R.f. *n*-hexane/EtOAc 8:2 = 0.21) yielded **4j** (80.6 mg, 87 %) as a white solid. M. p. = 88.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (brs, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 1.9 Hz, 1H), 7.34–7.01 (m, 9H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.20 (dd, *J* = 15.8, 6.7 Hz, 1H), 5.83 (d, *J* = 6.8 Hz, 1H), 4.26–3.94 (m, 1H), 3.58–3.14 (m, 1H), 2.63 (dt, *J* = 8.9, 5.0 Hz, 2H), 2.31 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4 (C_q), 137.5 (C_q), 135.6 (C_q), 134.4 (C_q), 133.6 (CH), 131.9 (C_q), 129.5 (CH), 128.5 (CH), 128.2 (CH), 127.7 (C_q), 127.0 (CH), 126.7 (CH), 125.7 (CH), 125.2 (C_q), 122.4 (CH), 117.8 (CH), 112.1 (CH), 108.6 (C_q), 54.6 (CH), 39.8 (CH_2), 21.4 (CH_3), 20.7 (CH_2). **(ESI) MS** calcd for $C_{26}H_{24}ClN_2O_2S$ ($[M+H]^+$) 463.12, found 463.11.

(*E*)-7-Chloro-1-(prop-1-en-1-yl)-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4k): The representive procedure **B** was followed using **2k** (140.0 mg, 0.36 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.67) yielded **4k** (74.2 mg, 51%) as a yellow solid. M. p. = 73.3 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (bs, 1H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.30-7.26 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.04 (dd, *J* = 8.6, 1.6 Hz, 1H), 5.70-5.49 (m, 3H), 4.12-4.04 (m, 1H), 3.34-3.24 (m, 1H), 2.64-2.56 (m, 2H), 2.35 (s, 3H), 1.64 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 137.8 (C_q), 136.4

(C_q), 131.9 (C_q), 130.4 (CH), 129.5 (CH), 128.0 (CH), 127.7 (C_q), 127.0 (CH), 125.3 (C_q), 120.0 (CH), 119.0 (CH), 111.0 (CH), 108.5 (C_q), 54.5 (CH), 39.7 (CH_2), 21.5 (CH_3), 20.8 (CH_2), 17.6 (CH_3). **(ESI) MS** calcd for $C_{21}H_{21}ClN_2NaO_2S$ $[M+Na]^+$ 423.09 found 423.22.

4,4'-bis((E)-2-(6-methoxy-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)vinyl)-1,1'-biphenyl (6a): The representive procedure **B** was followed using **5a** (71.4 mg, 0.08 mmol), $Pd(PPh_3)_4$ (20 mol %, 0.016 mmol), PPh_3 (40 mol %, 0.032 mmol) and BzOH (60 mol %, 0.048 mmol). Purification by chromatography on silica gel (R_f n-hexanes/acetone 6:4 = 0.07) yielded **6a** (39.8 mg, 56%) as a yellow solid. M. p. = 130.8 °C. **^{1}H NMR** (400 MHz, *d_6*-acetone) δ 10.5 (bs, 1H), 7.78-7.69 (m, 4H), 7.64-7.59 (m, 3H), 7.57-7.50 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.24-7.18 (m, 3H), 6.93 (d, *J* =2.4 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.61 (d, *J* = 15.6 Hz, 1H), 6.39 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.85 (d, *J* = 6.8 Hz, 1H), 4.24-4.17 (m, 1H), 3.78 (s, 3H), 3.52-3.42 (m, 1H), 2.72-2.65 (m, 2H), 2.27 (s, 3H). **^{13}C NMR** (101 MHz, *d_6*-acetone) δ 154.1 (C_q), 143.1 (C_q), 139.6 (C_q), 138.6 (C_q), 135.6 (C_q), 133.9 (rotA, C_q), 132.9 (rotB, C_q), 132.0 (rotA, C_q), 132.0 (rotB, C_q), 131.9 (CH), 131.9 (rotA, CH), 131.8 (rotB, CH), 129.4 (CH), 128.8 (rotA, CH), 128.6 (rotB, CH), 127.2 (CH), 127.0 (C_q), 126.7 (CH), 111.8 (CH), 111.5 (CH), 107.6 (C_q), 100.1 (CH), 55.1 (CH_3), 55.0 (CH), 40.2 (CH_2), 20.9 (CH_3), 20.4 (CH_2). **(ESI) MS** calcd for $C_{54}H_{50}K_2N_4O_6S_2$ $[M+2K]^+$ 992.25 found 992.28.

2-Tosyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (8a): The representive procedure **B** was followed using **7a** (70.4 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f n-hexanes/EtOAc 6:4 = 0.72) yielded **8a** (49.1 mg, 57%) as a yellow solid. M. p. = 82.3 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (bs, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 1H),

7.33 (d, *J* = 8.0 Hz, 1H), 7.21-7.16 (m, 3H), 7.13-7.08 (m, 1H), 6.01 (ddd, *J* = 17.0, 10.4, 6.2 Hz, 1H), 5.65 (d, *J* = 6.2 Hz, 1H), 5.28 (dt, *J* = 10.4, 1.0 Hz, 1H), 5.23 (dt, *J* = 17.0, 1.0 Hz, 1H), 4.09 (dt, *J* = 14.0, 3.6 Hz, 1H), 3.35 (dt, *J* = 14.0 8.4 Hz, 1H), 2.65 (dd, *J* = 8.4, 3.6 Hz, 2H), 2.36 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 137.9 (C_q), 136.1 (C_q), 135.3 (CH), 130.2 (C_q), 129.6 (CH), 127.0 (CH), 126.7 (C_q), 122.2 (CH), 119.6 (CH), 118.5 (CH), 118.3 (CH), 111.0 (CH), 109.1 (C_q), 55.0 (CH_2), 39.9 (CH_2), 21.5 (CH_3), 20.8 (CH_2). **(ESI) MS** calcd for $C_{20}H_{21}N_2O_2S$ $[M+H]^+$ 353.13 found 353.28.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-4-methyl-*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (8b'): The representive procedure **B** was followed using **7b** (76.0 mg, 0.20 mmol). Purification by chromatography on silica gel (R_f *n*-hexanes/EtOAc 6:4 = 0.84) yielded **8b'** (50.7 mg, 67%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.36-7.21 (m, 4H), 7.23-7.18 (m, 1H), 7.09 (d, *J* = 13.9 Hz, 1H), 6.94 (s, 1H), 6.41 (dt; *J* = 16.9, 10.4 Hz, 1H), 5.70 (dd, *J* =13.9, 10.4 Hz, 1H), 5.12 (d, *J* = 16.9 Hz, 1H), 5.02 (d, *J* = 10.4 Hz, 1H), 3.78 (s, 3H), 3.69-3.61 (m, 2H), 3.15-3.09 (m, 2H), 2.44 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.9 (C_q), 137.0 (C_q), 136.1 (C_q), 134.9 (CH), 129.9 (CH), 129.8 (CH), 127.6 (C_q), 126.9 (CH), 126.8 (CH), 121.8 (CH), 119.1 (CH), 118.8 (CH), 113.6 (CH), 111.5 (CH), 110.7 (C_q), 109.4 (CH), 46.5 (CH_2), 32.7 (CH_3), 23.6 (CH_2), 21.6 (CH_3). **(ESI) MS** calcd for $C_{22}H_{24}KN_2O_2S$ $[M+K]^+$ 419.12 found 419.17.

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4 Bi-directional isomerization to 1,3-Dienes

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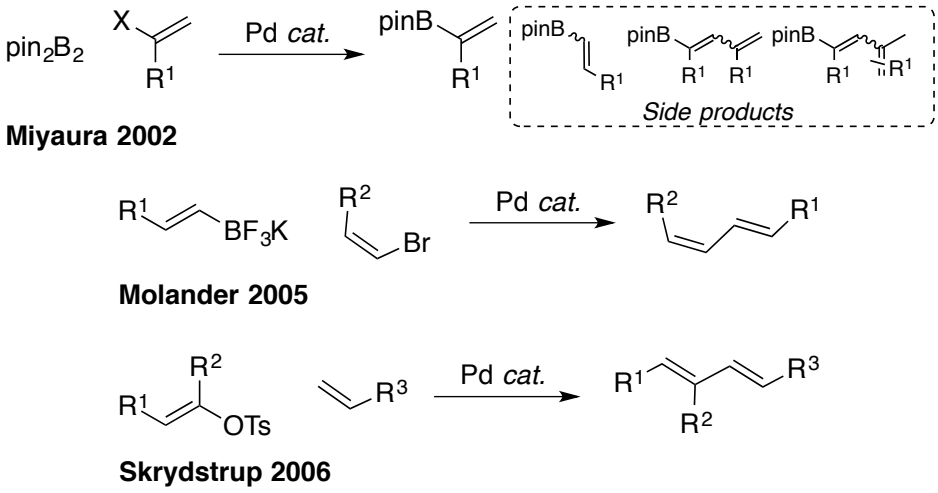
4.1 Introduction

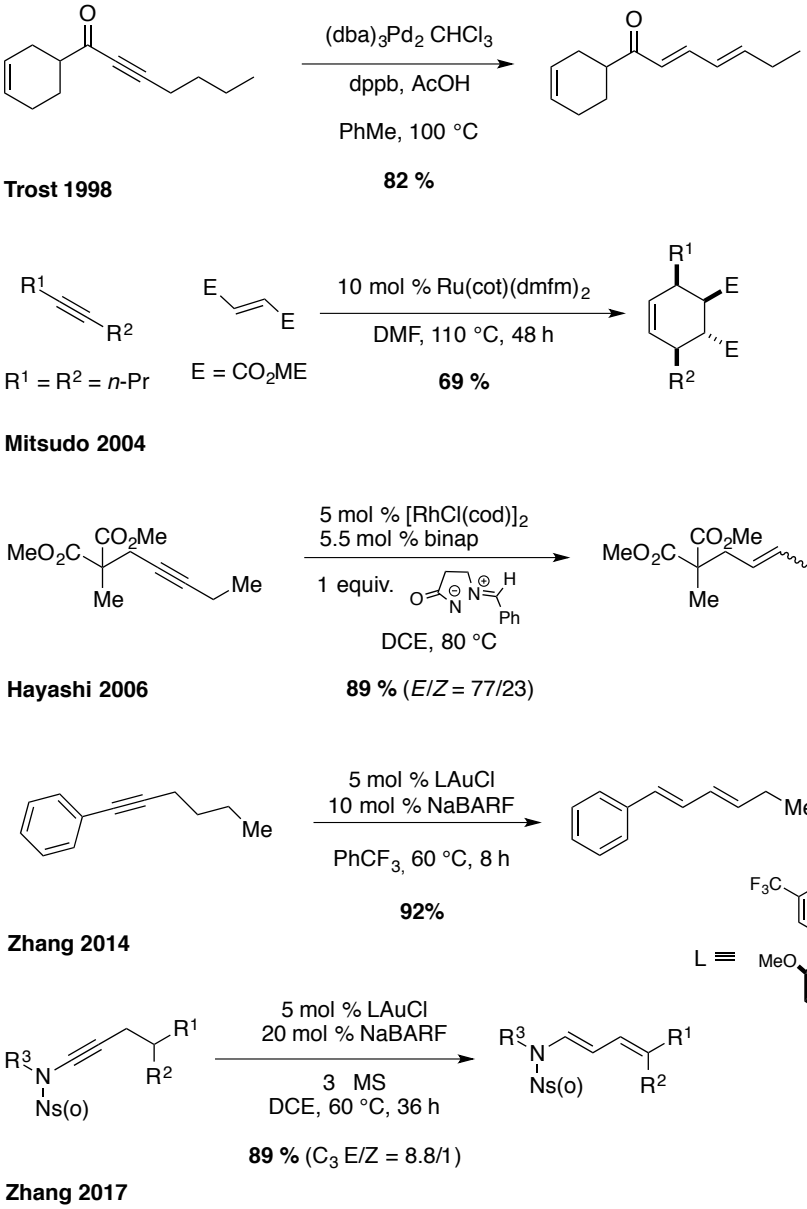
Conjugated 1,3-dienes are an important class of building blocks in organic chemistry, commonly employed in synthetic transformations to complex targets and commonly present in biologically active compounds. [152] A class of 1,3-dienes is represented by 1-amido-1,3-dienes. They can be considered as a stabilized *N*-delivering structural motif whose use in intra- and inter-molecular Diels-Alder cyclizations is widely established. [153–156] Diels-Alder reactions find a wide application in total synthesis of natural products. [157] However, the synthetic potential of 1-amido-1,3-dienes has not been fully grasped yet, mainly because of the lack of simple and robust synthetic methods to access them. The traditional metal-catalyzed C-C or C-N cross coupling reactions, already described in the introduction, suffer from the inherent limitations connected with the synthesis of halodienes or vinyl halides. This is coupled with issues in the stereochemical control of both reagents and products. [158]



Scheme 24 Examples of palladium cross-coupling reaction to 1,3-dienes

Indeed, Miyaura reported the first handy protocol of carbon-boron cross coupling to prepare boronate alkenes from vinyl halides and pin_2B_2. In this case, he observed a mixture of products, such as Heck and homocoupling side products, which are 1,3-dienes too. [15] The instability of boronate towards polymerization reactions lead Molander to use trifluorovinylboronates in a stereospecific palladium cross-coupling synthesis of conjugated 1,3-dienes. Unfortunately, this protocol cannot be applied to amino dienes. [159] In 2006, Skrydstrup report a Heck reaction of dienes that engage a vinyl reaction partner. [160]

An alternative, atom-economical approach relies on metal-catalyzed alkyne isomerizations. [161,162] Palladium catalyzed alkyne isomerization was illustrated by Trost. He reported a generation of palladium hydride with weak acid and palladium (0), which can generate a π-allyl species, which then undergoes β-elimination to form a 1,3-diene. However, substrates need strongly electron-withdrawing (EWG) groups alpha to the triple bond. [163]



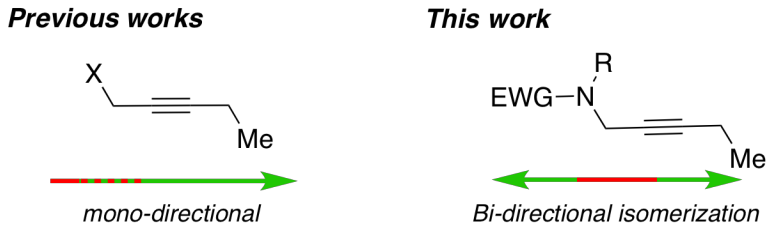
Scheme 25 Examples of Isomerization of alkynes to 1,3-dienes

Rare examples based on ruthenium, rhodium or gold catalysis are known. For examples, Mitsudo report the cascade reaction employing internal alkynes and dimethyl fumarate to achieve the cycloaddition products in presence of a ruthenium catalyst. [164] A plausible mechanism reported is divided in two step,

first isomerization of alkynes to 1,3-dienes catalyzed by the ruthenium hydride, followed by second Diels-Alder reaction that engage the electron poor alkenes. In 2006, Hayashi reported the unidirectional isomerization of alkynes using rhodium catalyst, but this protocol suffers from a limited stereocontrol, the mixture of products *E* and *Z* being recovered. [165] More recently, Zhang reported gold catalysis as a good alternative, employing gold(I) catalyst with a new bulky ligand. [166,167] Nevertheless, these methodologies suffer from the cost of elaborate ligands to afford desired dienes and did not show complete stereoselectivity to *E*,*E*-dienes (Scheme 2).

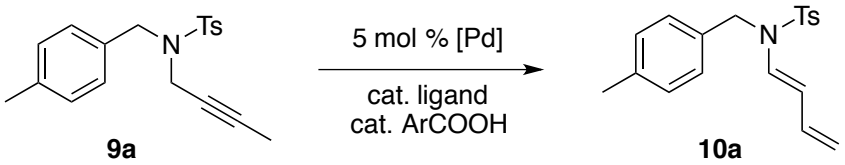
4.2 Results and discussion

During our studies on palladium-catalyzed cascades of alkyne derivatives, [168] we serendipitously disclosed that combination of palladium (0) with cheap benzoic acid can promote a tandem isomerization of propargylamides to form 1,3-dienes with high regiocontrol.



This catalytic combination was already known in literature to be able to form a palladium π-allyl complex from palladium (0) in presence of a protic acid, which can undergo a variety of reactions, as shown in Tsuji-Trost allylations. [124,169–171] Present catalytic system promoted an unprecedented bi-directional isomerization involving the two α-C(sp_3) of a 2-butynyl fragment to form diene instead. This is in sharp contrast with well-established isomerizations in which the electron density of the π-system extends in a single direction. [172] Reported "chain-walk" mechanisms were unidirectional only. [173,174] Present unique double isomerization of a 2-butyne fragments is thus complimentary to existing routes.

Moreover, this handy methodology presents a more straightforward reagent synthesis. Indeed, our reagents were synthetized through two steps at most.



9a **10a**

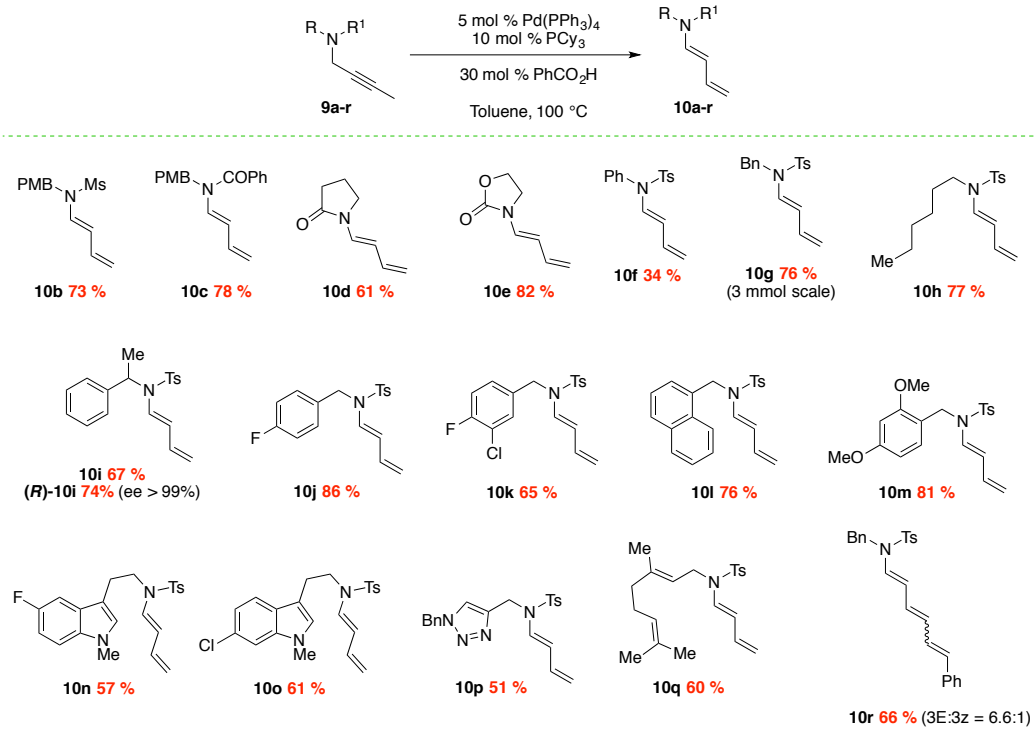
Entry	[Pd]	Ligand	Additive	Yield of 2a [%]
1	$Pd(PPh_3)_4$	PPh_3	$PhCO_2H$	78[a]
2	$Pd(PPh_3)_4$	--	$PhCO_2H$	71[b]
3	$Pd(dba)_2$	PPh_3	$PhCO_2H$	66[b]
4	$Pd(PPh_3)_4$	dppe	$PhCO_2H$	56[b]
5	$Pd(PPh_3)_4$	Davephos	$PhCO_2H$	59[b]
6	**$Pd(PPh_3)_4$**	**PCy_3**	**$PhCO_2H$**	**87**
7	$Pd(PPh_3)_4$	PPh_3	$PivCO_2H$	44[b]
8	$Pd(PPh_3)_4$	PPh_3	$MesCO_2H$	83[b]
9	$Pd(PPh_3)_4$	PCy_3	$MesCO_2H$	85
10	$Pd(PPh_3)_4$	PCy_3	2-furylCO_2H	80[b]
11	$Pd(PPh_3)_4$	PCy_3	4-$FC_6H_4CO_2H$	84
12	**$Pd(PPh_3)_4$**	**PCy_3**	**$PhCO_2H$**	**85[c]**

[a] Conditions: **1a** (0.20 mmol), [Pd] (0.01 mmol), ligand (0.02 mmol), $ArCO_2H$ (0.06 mmol), toluene (0.1 M, 2.0 ml), 100 °C, 16 h, isolated yields. [b] ^1H NMR yields determined with 1,4-dimethoxybenzene as internal standard. [c] [Pd] (0.06 mmol, 3.0 mol%), PCy_3 (0.012 mmol, 6.0 mol%). PMB = *p*Me-benzyl

At the outset of our studies, we submitted substrate **9a** to different ligands in the presence of catalytic $Pd(PPh_3)_4$ and benzoic acid. Monodentate phosphine performed better with respect to their bidentate analogues, promoting the formation of the corresponding diene **10a** in moderate to good yields (entries 1-5). Electron-rich PCy_3 showed improved competence providing the amidodiene (*E*)-**10a** in 87% yield and high stereocontrol (> 25:1, entry 6). Different carboxylic acid derivatives were then tested (Entries 7-11); beside weaker pivalic acid (44%, entry 7), we did not note however a marked electronic effect compared to user-friendly benzoic acid, which seemed therefore the most convenient hydride source for the reaction (Entries 8-11). Finally, a reaction conducted with a catalyst loading as low as 3% led to the isolation of **10a** in 85%

yield, further showing the high efficiency of the optimized catalytic system (entry 12).

We next studied the scope of the reaction submitting a family of propargylic amides **9** to the Pd-catalyzed tandem isomerization reaction. The methodology was found broadly applicable in the presence of different *N*-protected sulphonamides as well as benzamide and lactone derivatives **9b-e** (61-78%). Importantly, the oxazolidinone **9e** was delivered with high competence (82%).

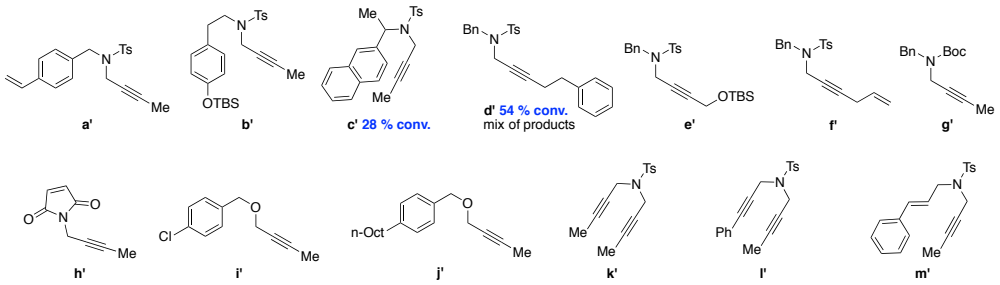


Scheme 26 Scope of reaction

Alkyl and aryl fragments ware found well tolerated, leading to products **10f-h** (34 - 77 %). The robustness of the methodology was reflected by a 3 mmol scale

dienamide synthesis (**10g**, 76%), which was isolated with a comparable yield in respect to the model reaction conducted on a 0.2 mmol scale.

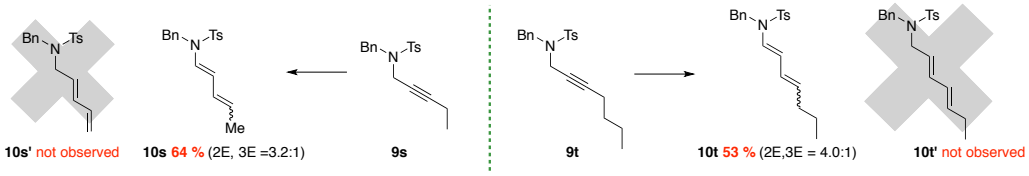
Noteworthy, the protocol prevents any racemization, allowing for the synthesis of the enantiomerically enriched amido-diene (*R*)-**10i** in 74% yield. Differently substituted benzylamine derivatives, including fluorinated and chlorinated ones, were found to be tolerated with the amido-dienes **10j**-**m** isolated in very good yields (65-86%). Different heterocycles such as tryptamine and triazole-based propargyl amide derivatives were converted in to the corresponding products **10n**-**p** in synthetically useful yields by using PPh_3 as ligand in the catalytic protocol (51-61%). Importantly, the high chemoselectivity of the described methodology was highlighted by the functional group tolerance with respect to the highly reactive geranyl fragment, with the synthesis of tetraene **10q** accomplished in good yields and no traces of any cycloisomerization product were observed (60%). [175,176] Finally, conjugated amido-triene **10r** could be isolated with good competence (66%).



Scheme 27 Unsuccessful substrate

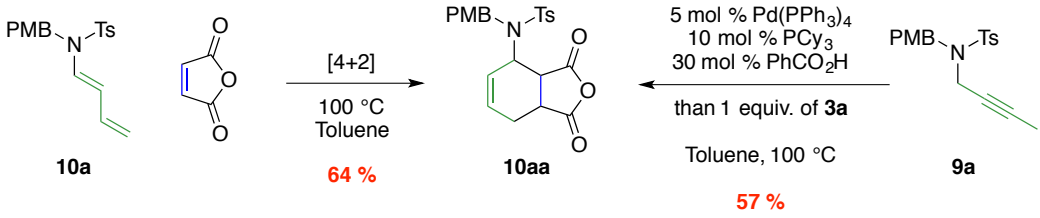
We also engaged further functionality on our substrates, such as aryl moieties on **a'-c'** and propargyl substitution of **d'-f'**. Unfortunately, we have observed low or no conversion of these reagents. We then examined further protecting groups and tether **g'-j'**, but reagents were quantitatively recovered. We also employing

polyunsaturated reagents **k'-m'**. Once more, we recovered only starting materials.



Scheme 28: Bidirectional isomerization

Noteworthy, the bi-directional nature of the palladium/benzoic acid-catalyzed isomerization was reflected when employing 2-pentyne **9s** and 2-octyne **9t** fragments. Indeed, the synthesis of *2E,3E*-amido-dienes **10s** and **10t** was accomplished with complete chemoselectivity and moderate levels of regioselectivity (*E*/*Z* up to 4:1).

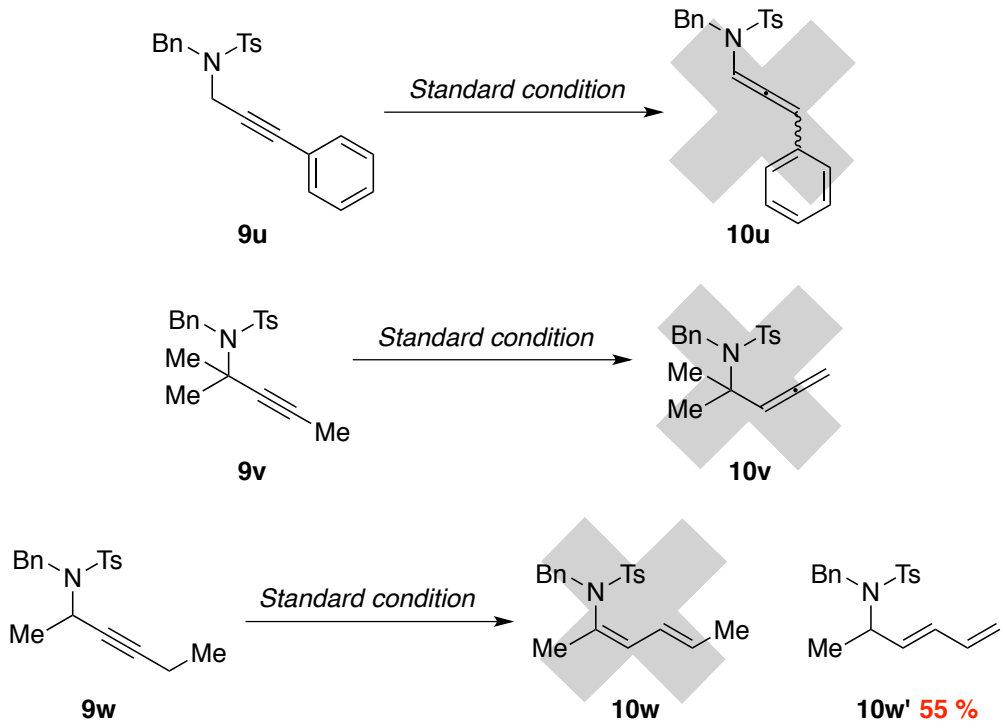


Scheme 29 Derivatization via Diels-Alder reactions

We than investigate the use of these 1,3-dienes. Amido diene **10a** was engaged in a [4+2] Diels-Alder cycloaddition reaction to prove the synthetic utility of the method. Bicycle **10aa** was retrieved in good yields and high diastereocontrol (64%, dr > 20:1). Hence, a one-pot strategy from propargylamide **9a** was possible, leading to the corresponding product **10aa** with comparable efficacy.

To rationalize the formation of 1,3-dienes, we reasoned that it would have involved the intermediate formation of an allene. Thus, we submitted propargyl

amide **9u** to the optimized catalytic system to form allenamide **10u**. However, we disappointingly saw no conversion. We thus prepared **9v**, aiming to trap the kinetically favoured allene **10v** instead. Surprisingly, this reagent too followed suit. However, while these two substrates failed in delivering any product, **9w**, which bears a tertiary carbon alpha to nitrogen, led surprisingly to diene **10w'**, although in moderate yields (Scheme 4, 55%).

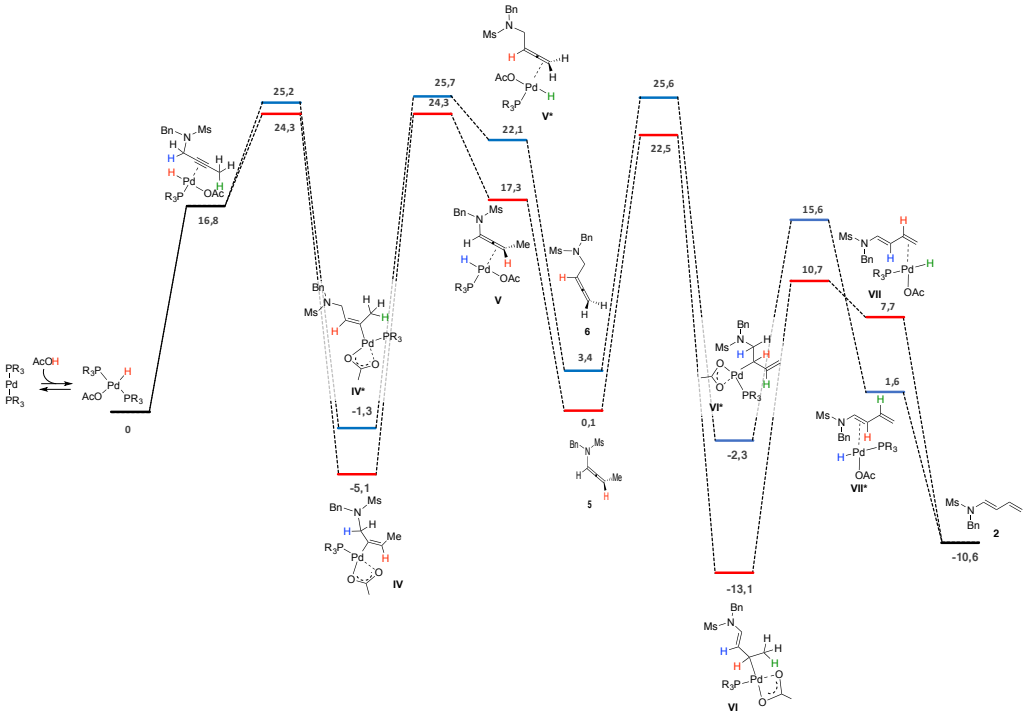


Scheme 30: Propargyl amines isomerization

This result led to hypothesize that the directionality of the tandem isomerization is strongly influenced by sterically demanded substrates. Thus, in order to get clear-cut insights in to the mechanism of these reactions, we resorted to DFT to check their multiple competing pathways. We analyzed the complete sequences leading to model diene **9a** (Figure 2) at the M06/Def2-svp(d) level using toluene

as implicit solvent. [177,178] This model proved efficient to rationalize the behavior of elaborate palladium species. [141,179]

Upon reversible *in-situ* formation of the palladium hydride **II**, ligand exchange with a molecule of **1** delivers complex **III**, which is less stable than the entry channel by +16.8 kcal/mol in ΔG. Product **2** can then form through two competing pathways. They depend on the regioselectivity of the first insertion on complex **III**. Each manifold involves twice a sequential hydride-transfer/β-elimination. Barriers for the former transition states (values between +3 and +8 kcal/mol) are lower than those of the latter in all these four sub-sequences (barriers between +18 and +29 kcal/mol).



Scheme 31 Most favourable modelled mechanism

In particular, β-eliminations from vinylpalladium complexes are the most demanding (ΔG +29.4 and +27.0 kcal/mol for **TS(IV-V)** and **TS(IV-V)***, respectively), followed by the β-elimination involving the terminal methyl group (+23.8 kcal/mol for **TS(VI-VII)**). The relatively most favorable β-elimination of the series involve the methylene *alpha* to nitrogen (+17.8 kcal/mol for **TS(VI-VII)***). These computational results are thus consistent with the stereoselectivity observed with substrates **9r** and **9s**. These reagents selectively afforded the corresponding dienamide only, leaving their terminal methyl group untouched and showing therefore that present bi-directional π-rearrangement is orthogonal to literature examples.

Interestingly, all σ-complex are more stable than the entry channel (**IV**, **IV***, **VI*** and **VI****, by -1–13 kcal/mol). This suggests that these intermediates are the least reactive ones in the reaction medium and could even represent catalytic dead-ends. On the contrary, all π-complex are less stable than the combination of the staring catalyst and **1** (**III**, **V**, **V***, **V****, **VII** and **VII***, by +2–25 kcal/mol). Among these, the two final intermediates **VII** and **VII*** are the relatively more stable ones, followed by the initial complex **III** (+7.7, +1.6 and +16.8 kcal/mol respectively). Furthermore, both allenamide **5** and allene **6** are less stable than propargyl amide **1**. This fits with the experimental failure to synthesize the corresponding products using reagents that could not evolve into 1,3-dienes (**1t-u**, Figure 4). Dienamide **2** is the sole thermodynamically favoured isomer of **1** (by -10.6 kcal/mol), ultimately ensuring the catalytic turnover by dictating the driving force of the dual isomerization and further highlighting its inherent synthetic challenges.

This trend is confirmed modeling reagent **9r**, which has a 2-pentyne chain. Its allene isomers parallel the outcome of their peers and the two dienes **2r** and **2r'** are the sole thermodynamically favorable isomers. The dienamide is the most

stable one (by 7.2 kcal/mol in ΔG), in perfect agreement with the complete absence of **2r'** observed experimentally.

4.3 Conclusion

We reported a simple catalytic system to convert easily-available alkynes in to the corresponding 1,3-dienamides through an unprecedented bidirectional tandem isomerization. The reaction is a convenient tool to access valuable products, which can be easily engaged in further sequences. Mixing experimental probes with DFT modelling, we rationalized the present reactivity on the basis of thermodynamic convenience towards the most stable alkyne isomer.

4.4 Experimental section

General procedure A for the synthesis of reagents: In a Schlenk flask, 1-Bromo-2-butyne (1.5 equiv) was added dropwise to a solution of the corresponding *N*-substituted-Tosylamide (1.0 equiv) and K_2CO_3 (1.5 equiv) in acetone (10 ml). Subsequently, the mixture was placed in a pre-heated oil bath at 50 °C and stirred overnight. After completion, the reaction mixture was cooled down to room temperature and sat. NH_4Cl (15 ml) was added. The mixture was extracted with EtOAc (3 x 15 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.

General procedure B for the synthesis of reagents: In an oven-dried two-necked round-bottomed flask, the corresponding propargylic alcohol derivative (1.2 equiv) was added to a 1.0 M solution in THF of the corresponding *N*-substituted-Tosylamide (1.0 equiv) and PPh_3 (1.2 equiv) under N_2 atmosphere. Subsequently, the mixture was placed at 0°C and DIAD (1.2 equiv) was carefully added dropwise over 10 min. The mixture was stirred until complete conversion (2-8 hs). Subsequently, a solution of HCl (0.1 M, 10 ml) was added, the mixture extracted with EtOAc (3 x 15 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.

General procedure C for the synthesis of dienes: In an oven dried tube, **1** (0.20 mmol), $Pd(PPh_3)_4$ (0.01 mmol), PCy_3 (0.02 mmol) and BzOH (0.06 mmol) were added sequentially and purged with nitrogen three times. Subsequently, toluene (2.0 ml, 0.1 M) was added under N_2 atmosphere and the tube placed in a pre-heated oil bath at 100 °C overnight (16 hs). The reaction mixture was then cooled

down at room temperature and CH_2Cl_2 (10 ml) was added. The mixture was concentrated under reduced pressure and the crude purified by chromatography on silica gel.

***N*-Benzyl-*N*-(but-2-yn-1-yl)methanesulfonamide (9b)**: Representative procedure **A** was followed using *N*-Benzylmethanesulfonamide (185 mg, 1.0 mmol) and 1-Bromo-2-butyne (198 mg, 1.5 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9b** (207 mg, 87 %) as a white solid. **M. p.** = 60.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (5H), 4.41 (s, 2H), 3.86 (q, *J* = 2.4 Hz, 2H), 3.00 (s, 3H), 1.88 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.1 (C_q), 128.7 (CH), 128.7 (CH), 128.1 (CH), 82.4 (C_q), 72.2 (C_q), 49.8 (CH_2), 38.2 (CH_2), 35.9 (CH_3), 3.5 (CH_3). **(ESI) MS** calcd for $C_{14}H_{19}N_2O_2S$ $[M+CH_3CN+H]^+$ 279.12 found 279.24.

***N*-(But-2-yn-1-yl)-N-(4-methylbenzyl)benzamide (9c)**: To a solution of *N*-(4-methylbenzyl)benzamide (500 mg, 2.2 mmol) in THF (10 ml), NaH (60% in mineral oil) (132 mg, 3.3 mmol) was added at 0°C and the mixture stirred at the same temperature for 30 min. Subsequently, 1-Bromo-2-butyne (435 mg, 3.3 mmol) was added and the reaction mixture stirred overnight. A solution of HCl (0.1 M, 10 ml) was added, the mixture extracted with EtOAc (3 x 15 ml) and the organic layers separated and dried over Na_2SO_4. The combined fractions were concentrated under reduced pressure and the crude purified by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielding **9c** (472 mg, 77%) as an orange solid. **M. p** = 65.6 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62-7.49 (m, 3H), 7.48-7-29 (m, 3H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.14-7.08 (m, 1H), 4.87 – 4.80 (m, 1H), 4.68 – 4.57 (m, 1H), 4.34 – 4.14 (m, 1H), 3.83 (s, 1H), 2.37 (s, 3H), 1.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4 (C_q, rotA), 163.7 (C_q, rotB), 137.3 (C_q), 136.7 (CH), 129.9 (C_q), 129.4 (CH), 129.0 (CH), 128.8 (C_q),

128.5 (CH), 127.01 (CH), 77.2 (C_q), 73.76 (C_q), 51.4 (CH_2, rotA), 47.10 (CH_2, rotA), 38.5 (CH_2, rotA), 33.7 (CH_2, rotB), 21.1 (CH_3), 3.6 (CH_3). **(ESI) MS** calcd for $C_{19}H_{20}NO$ $[M+H]^+$ 278.15 found 278.11.

***N*-(But-2-yn-1-yl)-4-methyl-*N*-phenylbenzenesulfonamide (9f)**: Representative procedure **A** was followed using 4-Methyl-*N*-phenylbenzenesulfonamide (494 mg, 2.0 mmol) and 1-Bromo-2-butyne (396 mg, 3.0 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9f** (523 mg, 87%) as a white solid. **M. p.** = 84.8 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.09 (m, 7H), 4.40 (q, *J* = 2.3 Hz, 2H), 2.43 (s, 3H), 1.68 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.4 (C_q), 139.9 (C_q), 135.9 (C_q), 129.1 (CH), 128.9 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 81.7 (C_q), 73.4 (C_q), 41.7 (CH_2), 21.6 (CH_3), 3.5 (CH_3). **(ESI) MS** calcd for $C_{17}H_{18}NO_2S$ $[M+H]^+$ 300.11 found 300.17.

***N*-(But-2-yn-1-yl)-*N*-hexyl-4-methylbenzenesulfonamide (9h)**: Representative procedure **A** was followed using *N*-Hexyl-4-methylbenzenesulfonamide (510 mg, 2.0 mmol) and 1-Bromo-2-butyne (396 mg, 3.0 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9h** (462 mg, 75%) as an oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.06 (q, *J* = 2.3 Hz, 2H), 3.23 – 3.04 (m, 2H), 2.42 (s, 3H), 1.62 – 1.45 (m, 5H), 1.35-1-20 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.0 (C_q), 136.2 (C_q), 129.2 (CH), 127.8 (CH), 81.3 (C_q), 71.8 (C_q), 46.2 (CH_2), 36.6 (CH_2), 31.4 (CH_2), 27.5 (CH_2), 26.2 (CH_2), 22.5 (CH_2), 21.5 (CH_3), 14.0 (CH_3), 3.2 (CH_3). **(ESI) MS** calcd for $C_{17}H_{26}NO_2S$ $[M+H]^+$ 308.17 found 308.20.

***N*-(But-2-yn-1-yl)-4-methyl-*N*-(1-phenylethyl)benzenesulfonamide (9i)**: Representative procedure **A** was followed using 4-Methyl-*N*-(1-phenylethyl)benzenesulfonamide (495 mg, 1.8 mmol) and 1-Bromo-2-butyne (359 mg, 2.7 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9i** (502 mg, 85%) as a whitish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.87 (m, 2H), 7.38 – 7.26 (m, 7H), 5.25 (q, *J* = 7.2 Hz, 1H), 4.13 (dd, *J* = 18.4, 2.7 Hz, 1H), 3.74 – 3.38 (m, 1H), 2.46 (s, 3H), 1.64 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.0 (C_q), 139.7 (C_q), 138.2 (C_q), 129.2 (CH), 128.3 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 80.3 (C_q), 75.1 (C_q), 55.7 (CH), 33.0 (CH_2), 21.5 (CH_3), 16.8 (CH_3), 3.3 (CH_3). **(ESI) MS** calcd for $C_{19}H_{21}NNaO_2S$ $[M+Na]^+$ 350.12 found 350.19.

***N*-(But-2-yn-1-yl)-*N*-(4-fluorobenzyl)-4-methylbenzenesulfonamide (9j)**: Representative procedure **B** was followed using *N*-(4-Fluorobenzyl)-4-methylbenzenesulfonamide (350 mg, 1.25 mmol) and But-2-yn-1-ol (91 mg, 1.3 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9j** (274 mg, 66%) as a white sticky oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.31 (m, 4H), 7.01 (dd, *J* = 9.7, 7.7 Hz, 2H), 4.28 (s, 2H), 3.86 (q, *J* = 2.2 Hz, 2H), 2.44 (s, 3H), 1.54 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.71 (d, *J* = 246.5 Hz, C_q), 143.6 (C_q), 136.3 (C_q), 131.3 (d, *J* = 3.2 Hz, C_q), 130.6 (d, *J* = 8.2 Hz, CH), 129.5 (CH), 128.1 (CH), 115.69 (d, *J* = 21.5 Hz, CH), 82.2 (C_q), 71.5 (C_q), 49.3 (CH_2), 36.3 (CH_2), 21.7 (CH_3), 3.4 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.27. **(ESI) MS** calcd for $C_{18}H_{19}FNO_2S$ $[M+H]^+$ 332.11 found 332.15.

***N*-(But-2-yn-1-yl)-*N*-(3-chloro-4-fluorobenzyl)-4-methylbenzenesulfonamide (9k)**: Representative procedure **A** was followed using *N*-(3-Chloro-4-fluorobenzyl)-4-methylbenzenesulfonamide (563 mg, 1.8

mmol) and 1-Bromo-2-butyne (356 mg, 2.7 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9k** (544 mg, 83%) as a white solid. **M. p.** = 90.4 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.38 (dt, *J* = 6.7, 3.4 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.18 (m, 1H), 7.09 (t, *J* = 8.6 Hz, 1H), 4.26 (s, 2H), 3.88 (q, *J* = 2.2 Hz, 2H), 2.45 (s, 3H), 1.54 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.8 (d, $^{1}J_{C-F}$ = 249 Hz, C_q), 143.6 (C_q), 135.9 (C_q), 132.6 (d, *J* = 4 Hz, C_q), 130.8 (CH), 129.6 (CH), 128.4 (d, *J* = 7 Hz, CH), 128.1 (CH), 121.1 (d, *J* = 18 Hz, C_q), 116.7 (d, *J* = 21 Hz, CH), 82.3 (C_q), 71.2 (C_q), 48.9 (CH_2), 36.5 (CH_2), 21.5 (CH_3), 3.2 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.41. **(ESI) MS** calcd for $C_{18}H_{17}ClFKNO_2S$ $[M+K]^+$ 404.03 found 404.11.

***N*-(But-2-yn-1-yl)-4-methyl-*N*-(naphthalen-1-ylmethyl)benzenesulfonamide (9l)**: Representative procedure **A** was followed using 4-Methyl-*N*-(naphthalen-1-ylmethyl)benzenesulfonamide (555 mg, 1.8 mmol) and 1-Bromo-2-butyne (356 mg, 2.7 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9l** (544 mg, 83%) as a white solid. **M. p.** = 154.5 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.88 – 7.83 (m, 2H), 7.65 – 7.50 (m, 2H), 7.50 – 7.43 (m, 2H), 7.42 – 7.37 (m, 2H), 4.79 (s, 2H), 3.80 (q, *J* = 2.2 Hz, 2H), 2.50 (s, 3H), 1.55 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.4 (C_q), 135.5 (C_q), 133.9 (C_q), 132.1 (C_q), 130.1 (C_q), 129.3 (CH), 129.2 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 126.7 (CH), 126.1 (CH), 125.0 (CH), 124.4 (CH), 82.3 (C_q), 71.3 (C_q), 48.4 (CH_2), 36.1 (CH_2), 21.6 (CH_3), 3.3 (CH_3). **(ESI) MS** calcd for $C_{22}H_{22}NO_2S$ $[M+H]^+$ 364.14 found 364.18.

***N*-(But-2-yn-1-yl)-*N*-(2,4-dimethoxybenzyl)-4-methylbenzenesulfonamide (9m)**: Representative procedure **A** was followed using *N*-(2,4-

dimethoxybenzyl)-4-methylbenzenesulfonamide (481 mg, 1.5 mmol) and 1-Bromo-2-butyne (290 mg, 2.2 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9m** (448 mg, 80%) as a white solid. **M. p.** = 96.7 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.34-7.28 (m, 3H), 6.48 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 4.34 (s, 2H), 3.93 (d, *J* = 2.2 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 2.44 (s, 3H), 1.57 (t, *J* = 2.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.7 (C_q), 158.8 (C_q), 143.0 (C_q), 136.6 (C_q), 130.9 (CH), 129.1 (CH), 128.0 (CH), 116.0 (C_q), 104.2 (CH), 98.5 (CH), 81.3 (C_q), 72.2 (C_q), 55.4 (CH_3), 55.3 (CH_3), 44.3 (CH_2), 36.6 (CH_2), 21.5 (CH_3), 3.3 (CH_3). **(ESI) MS** calcd for $C_{20}H_{23}NaNO_4S$ $[M+Na]^+$ 396.12 found 396.18.

***N*-(But-2-yn-1-yl)-*N*-[2-(5-fluoro-1-methyl-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (9n)**: Representative procedure **A** was followed using *N*-[2-(5-fluoro-1-methyl-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (346 mg, 1.0 mmol) and 1-Bromo-2-butyne (198 mg, 1.5 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9n** (302 mg, 76%) as a white solid. **M. p.** = 114.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.23 (m, 2H), 7.23 – 7.13 (m, 2H), 7.00 (s, 1H), 6.99-6.94 (m, 1H), 4.15 (d, *J* = 2.3 Hz, 2H), 3.75 (s, 3H), 3.45 (dd, *J* = 8.9, 6.9 Hz, 2H), 3.02 (dd, *J* = 17.7, 9.6 Hz, 2H), 2.42 (s, 3H), 1.63 (t, *J* = 2.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6 (d, *J* = 235 Hz, C_q), 143.2 (C_q), 136.0 (C_q), 133.6 (C_q), 129.3 (CH), 128.7 (CH), 128.0 (d, *J* = 9 Hz, C_q), 127.8 (CH), 110.8 (d, *J* = 5Hz, C_q), 110.0 (d, *J* = 10 Hz, CH), 109.9 (d, *J* = 6 Hz, CH), 103.6 (d, *J* = 23 Hz, CH), 81.8 (C_q), 71.9 (C_q), 46.8 (CH_2), 37.2 (CH_3), 32.9 (CH_2), 24.0 (CH_2), 21.5 (CH_3), 3.2 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.9. **(ESI) MS** calcd for $C_{22}H_{23}KFN_2O_2S$ $[M+K]^+$ 437.11 found 437.15.

***N*-(But-2-yn-1-yl)-*N*-[2-(6-chloro-1-methyl-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (9o)**: Representative procedure **A** was followed using *N*-[2-(6-chloro-1-methyl-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (207 mg, 0.5 mmol) and 1-Bromo-2-butyne (100 mg, 0.75 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9o** (156 mg, 75%) as a yellow viscous oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.13 (m, 3H), 7.11 – 6.99 (m, 1H), 6.92 (s, 1H), 4.16 – 4.01 (m, 2H), 3.69 (s, 3H), 3.52 – 3.33 (m, 2H), 3.09 – 2.91 (m, 2H), 2.42 (s, 3H), 1.58 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.2 (C_q), 137.4 (C_q), 136.0 (C_q), 129.3 (CH), 127.8 (CH), 128.7 (C_q), 127.6 (CH), 126.3 (C_q), 119.7 (CH), 119.5 (CH), 111.3 (C_q), 109.3 (CH), 81.6 (C_q), 72.0 (C_q), 47.0 (CH_2), 37.3 (CH_3), 32.7 (CH_2), 24.1 (CH_2), 21.5 (CH_3), 3.3 (CH_3). **(ESI) MS** calcd for $C_{22}H_{23}ClKN_2O_2S$ $[M+K]^+$ 453.08 found 453.16.

***N*-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (9p):** Representative procedure **A** was followed using *N*-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl]methyl)-*N*,4-dimethylbenzenesulfonamide (200 mg, 0.6 mmol) and 1-Bromo-2-butyne (119 mg, 0.9 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9p** (204 mg, 86%) as a white solid. **M. p.** = 107.1 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.6 Hz, 2H), 7.52 (s, 1H), 7.39 – 7.36 (m, 3H), 7.29 – 7.27 (m, 4H), 5.50 (s, 2H), 4.47 (s, 2H), 3.99 (d, *J* = 2.6 Hz, 2H), 2.43 (s, 3H), 1.54 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.2 (C_q), 143.5 (C_q), 136.1 (C_q), 134.4 (C_q), 129.4 (CH), 129.2 (CH), 128.8 (CH), 128.1 (CH), 127.8 (CH), 122.9 (CH), 82.0 (C_q), 71.6 (C_q), 54.3 (CH_2), 41.9

(CH_2), 37.3 (CH_2), 21.5 (CH_3), 3.3 (CH_3). (ESI) MS calcd for $C_{21}H_{23}N_4O_2S$ $[M+H]^+$ 395.15 found 395.19.

(*E*)-*N*-(But-2-yn-1-yl)-*N*-(3,7-dimethylocta-2,6-dien-1-yl)-4-methylbenzenesulfonamide (9q): Representative procedure **A** was followed using (*E*)-*N*-(3,7-Dimethylocta-2,6-dien-1-yl)-4-methylbenzenesulfonamide (465 mg, 1.6 mmol) and 1-Bromo-2-butyne (317 mg, 2.4 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9q** (443 mg, 77%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.48 – 7.17 (m, 2H), 5.10 (t, *J* = 7.3 Hz, 1H), 5.05 (t, *J* = 6.3 Hz, 1H), 4.00 (d, *J* = 2.1 Hz, 2H), 3.80 (t, *J* = 8.5 Hz, 2H), 2.44 (s, 3H), 2.16 – 1.88 (m, 4H), 1.68 (s, 3H), 1.66 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.0 (C_q), 142.1 (C_q), 136.3 (C_q), 131.8 (C_q), 129.2 (CH), 127.9 (CH), 123.8 (CH), 118.1 (CH), 81.2 (C_q), 72.1 (C_q), 43.8 (CH_2), 39.6 (CH_2), 35.8 (CH_2), 26.2 (CH_3), 25.7 (CH_2), 21.5 (CH_3), 17.7 (CH_3), 16.1 (CH_3), 3.2 (CH_3). **(ESI) MS** calcd for $C_{21}H_{29}KNO_2S$ $[M+K]^+$ 398.16 found 398.22.

(*E*)-4-Methyl-*N*-(4-methylbenzyl)-*N*-(6-phenylhex-5-en-2-yn-1-yl)benzenesulfonamide (9r): Representative procedure **B** was followed using 4-Methyl-*N*-(4-methylbenzyl)benzenesulfonamide (412 mg, 1.5 mmol) and (*E*)-6-Phenylhex-5-en-2-yn-1-ol (328 mg, 1.8 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **1r** (380 mg, 59%) as a white oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.76 (m, 2H), 7.43 – 7.21 (m, 8H), 7.20 – 7.07 (m, 3H), 6.51 – 6.32 (m, 1H), 6.07 – 5.87 (m, 1H), 4.46 – 4.25 (m, 2H), 4.10 – 3.94 (m, 2H), 3.01 – 2.80 (m, 2H), 2.36 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4 (C_q), 137.8 (C_q), 136.9 (C_q), 136.2 (C_q), 132.0 (C_q), 131.3 (CH), 129.4 (CH), 129.3 (CH), 128.8 (CH), 128.6 (CH), 127.9 (CH), 127.5 (CH), 126.2 (CH), 123.6 (CH), 83.0 (C_q), 74.9 (C_q), 49.7

(CH_2), 36.0 (CH_2), 22.1 (CH_2), 21.4 (CH_3), 21.2 (CH_3). **(ESI) MS** calcd for $C_{27}H_{28}NO_2S$ $[M+H]^+$ 430.18 found 430.22.

***N*-Benzyl-4-methyl-*N*-(pent-2-yn-1-yl)benzenesulfonamide (9s)**: Representative procedure **A** was followed using *N*-Benzyl-4-methylbenzenesulfonamide (523 mg, 2.0 mmol) and 1-Bromo-2-pentyne (441 mg, 3.0 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9s** (568 mg, 87%) as a white solid. **M. p.** = 60.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.73 (m, 2H), 7.43 – 7.24 (m, 7H), 4.36 (s, 2H), 3.93 (t, *J* = 2.2 Hz, 2H), 2.46 (s, 3H), 1.94 (qt, *J* = 7.5, 2.2 Hz, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3 (C_q), 136.2 (C_q), 135.3 (C_q), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 87.9 (C_q), 71.5 (C_q), 49.8 (CH_2), 36.1 (CH_2), 21.5 (CH_3), 13.5 (CH_3), 12.1 (CH_2). **(ESI) MS** calcd for $C_{19}H_{21}KNO_2S$ $[M+K]^+$ 366.09 found 366.13.

***N*-Benzyl-*N*-(hept-2-yn-1-yl)-4-methylbenzenesulfonamide (9t)**: Representative procedure **B** was followed using *N*-Benzyl-4-methylbenzenesulfonamide (391 mg, 1.5 mmol) and Hept-2-yn-1-ol (202 mg, 1.8 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9t** (378 mg, 71%) as a white oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.44 – 7.19 (m, 7H), 4.33 (s, 2H), 3.91 (s, 2H), 2.44 (s, 3H), 1.91 (s, 2H), 1.32 – 1.08 (m, 4H), 0.85 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.3 (C_q), 136.3 (C_q), 135.3 (C_q), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 86.6 (C_q), 72.1 (C_q), 49.8 (CH_2), 36.1 (CH_2), 30.5 (CH_2), 21.9 (CH_2), 21.5 (CH_3), 18.1, 13.6 (CH_3). **(ESI) MS** calcd for $C_{21}H_{26}NO_2S$ $[M+H]^+$ 356.17 found 356.21.

***N*-Benzyl-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (9u):** Representative procedure **B** was followed using *N*-Benzyl-4-methylbenzenesulfonamide (522 mg, 2.0 mmol) and 3-Phenylprop-2-yn-1-ol (317 mg, 2.4 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9u** (475 mg, 66%) as a white solid. **M. p.** = 96.6 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.53 – 7.22 (m, 10H), 7.17 – 6.95 (m, 2H), 4.45 (s, 2H), 4.18 (s, 2H), 2.38 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6 (C_q), 136.0 (C_q), 135.1 (C_q), 131.5 (CH), 129.6 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 122.2 (C_q), 86.1 (C_q), 81.5 (C_q), 50.2 (CH_2), 36.5 (CH_2), 21.5 (CH_3). **(ESI) MS** calcd for $C_{23}H_{22}NO_2S$ $[M+H]^+$ 376.14 found 376.18.

***N*-Benzyl-4-methyl-*N*-(2-methylpent-3-yn-2-yl)benzenesulfonamide (9v)**: 4-Methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (560 mg, 2.3 mmol) and Benzylbromide (600 mg, 3.5 mmol) were stirred in a solution of K_2CO_3 (480 mg, 3.5 mmol) and acetone (10 ml) at 55 °C for 16 hs. The crude was purified by column chromatography (*n*-hexanes/EtOAc 80:20) yielding *N*-Benzyl-4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (576 mg, 50 %) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.28 (dd, *J* = 8.3, 5.9 Hz, 4H), 4.85 (s, 2H), 2.43 (s, 3H), 2.29 (s, 1H), 1.63 (s, 6H). *N*-Benzyl-4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (576 mg, 1.75 mmol) was dissolved in dry THF (10 ml) under inert atmosphere and the solution cooled down at -78 °C. Subsequently, *n*-BuLi (1.6 M, 1.64 ml, 2.6 mmol) was added dropwise over 30 min and mixture stirred for additional 30 min at the same temperature. Hence, MeI (369 mg, 2.6 mmol) was added in one pot and the reaction mixture stirred overnight. After completion, a solution of HCl (0.1 M, 10 ml) was added, the mixture extracted with EtOAc (3 x 15 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 yielding **9v** (485 mg, 72 %) as a yellow solid. **M. p.** = 67.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.21 (m, 3H), 4.80 (s, 2H), 2.43 (s, 3H), 1.61 (s, 3H), 1.58 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.7 (C_q), 139.9 (C_q), 139.5 (C_q), 129.1 (CH), 128.2 (CH), 127.5 (CH), 127.5 (CH), 126.9 (CH), 81.7 (C_q), 80.0 (C_q), 57.4 (C_q), 52.0 (CH_2), 31.2 (CH_3), 21.5 (CH_3), 3.4 (CH_3). **(ESI) MS** calcd for $C_{20}H_{24}NO_2S$ $[M+H]^+$ 342.15 found 342.28.

***N*-Benzyl-*N*-(hex-3-yn-2-yl)-4-methylbenzenesulfonamide (9w):** Representative procedure **B** was followed using *N*-Benzyl-4-methylbenzenesulfonamide (522 mg, 2.0 mmol) and Hex-3-yn-2-ol (216 mg, 2.2 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **9w** (402 mg, 56%) as a yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 2H), 7.37 – 7.21 (m, 5H), 4.93 (dtd, *J* = 7.1, 5.3, 2.0 Hz, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.21 (d, *J* = 16.0 Hz, 1H), 2.45 (s, 3H), 1.99 (qd, *J* = 7.5, 2.1 Hz, 2H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2 (C_q), 138.7 (C_q), 136.4 (C_q), 129.4 (CH), 128.3 (CH), 127.9 (CH), 127.7 (CH), 127.2 (CH), 87.5 (C_q), 76.6 (C_q), 48.3 (CH_2), 47.2 (CH), 23.3(CH_3), 21.5 (CH_3), 13.6 (CH_3), 12.1 (CH_2). **(ESI) MS** calcd for $C_{20}H_{24}NO_2S$ $[M+H]^+$ 342.15 found 342.18.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-4-methyl-*N*-(4-methylbenzyl)benzenesulfonamide (10a): Representative procedure **C** was followed using **9a** (65.4 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10a** (56.8 mg, 87%) as a yellow solid. **R_f** *n*-hexanes/EtOAc 8:2 = 0.58. **M. p.** = 83.6 °C. **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 7.70 (t, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 14.0 Hz, 1H), 6.24 (dt, *J* = 16.9, 10.3 Hz, 1H), 5.42 (dd, *J* = 14.0, 10.5 Hz, 1H), 4.92 (d, *J* = 16.9 Hz, 1H), 4.87 (d, *J* = 10.5 Hz, 1H), 4.53 (s, 2H), 2.44 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.0 (C_q), 137.2 (C_q), 136.0 (C_q), 134.7 (CH), 132.2 (C_q), 130.0 (CH), 129.9 (CH), 129.3 (CH), 127.0 (CH), 126.8 (CH), 113.8 (CH), 113.0 (CH_2), 49.3 (CH_2), 21.6 (CH_3), 21.1 (CH_3). **(ESI) MS** calcd for $C_{19}H_{21}NNaO_2S$ $[M+Na]^+$ 350.12 found 350.03.

(*E*)-*N*-Benzyl-*N*-(buta-1,3-dien-1-yl)methanesulfonamide (10b): Representative procedure **C** was followed using **9b** (44.6 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10b** (32.6 mg, 73%) as a yellow oil. **R_f** *n*-hexanes/EtOAc 8:2 = 0.35. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.13 (m, 5H), 6.88 (d, *J* = 14.0 Hz, 1H), 6.25 (dt, *J* = 16.9, 10.3 Hz, 1H), 5.58 (dd, *J* = 14.0, 10.4 Hz, 1H), 4.99 (t, *J* = 13.8 Hz, 1H), 4.93 (d, *J* = 10.3 Hz, 1H), 4.76 (s, 2H), 2.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.4 (C_q), 134.4 (CH), 129.5 (CH), 128.8 (CH), 127.8 (CH), 127.0 (CH), 114.3 (CH), 112.8 (CH_2), 49.4 (CH_2), 39.8 (CH_3). **(ESI) MS** calcd for $C_{14}H_{19}N_2O_2S$ $[M+CH_3CN+H]^+$ 279.12 found 279.37.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-*N*-(4-methylbenzyl)benzamide (10c): Representative procedure **C** was followed using **9c** (55.4 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10c** (43.4 mg, 78%) as an orange viscous oil. **R_f** *n*-hexanes/EtOAc 8:2 = 0.51. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61-7.43 (m, 5H), 7.26-7.14 (m, 4H), 6.80 (bs, 1H), 6.09 (bs, 1H), 5.73 (dd, *J* = 13.5, 10.9 Hz, 1H), 5.03 (d, *J* = 16.8 Hz, 2H), 4.92 (d, *J* = 10.0 Hz, 2H), 2.37 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7 (C_q), 136.9 (CH), 136.1 (C_q), 134.9 (C_q), 133.6 (C_q), 130.6 (CH), 129.5

(CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 126.7 (CH), 114.6 (CH), 112.9 (CH_2), 47.7 (CH_2), 21.1 (CH_3). **(ESI) MS** calcd for $C_{19}H_{20}NO$ $[M+H]^+$ 278.15 found 278.06.

(*E*)-1-(Buta-1,3-dien-1-yl)pyrrolidin-2-one (10d): Representative procedure **C** was followed using **9d** (54.8 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 70:30) yielded **10d** (33.4 mg, 61%) as a yellow solid. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.16. **M. p.** = 59.8 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 14.1 Hz, 1H), 6.35 (dt, *J* = 17.0, 10.4 Hz, 1H), 5.63 (dd, *J* = 14.2, 10.7 Hz, 1H), 5.14 (dd, *J* = 17.0, 1.8 Hz, 1H), 4.99 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.64 – 3.48 (m, 2H), 2.61 – 2.41 (m, 2H), 2.23 – 2.03 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.96 (C_q), 134.9 (CH), 126.7 (CH), 114.7 (CH), 112.9 (CH_2), 45.1 (CH_2), 31.2 (CH_2), 17.4 (CH_2). **(ESI) MS** calcd for $C_8H_{12}NO$ $[M+H]^+$ 138.09 found 138.18.

(*E*)-3-(Buta-1,3-dien-1-yl)oxazolidin-2-one (10e): Representative procedure **C** was followed using **9e** (27.8 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **10e** (22.8 mg, 82%) as a yellow oil. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.15. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 14.1 Hz, 1H), 6.31 (dt, *J* = 17.0, 10.4 Hz, 1H), 5.51 (dd, *J* = 14.0, 10.6 Hz, 1H), 5.11 (d, *J* = 16.9 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 4.54 – 4.30 (m, 2H), 3.83 – 3.59 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.4 (C_q), 134.3 (CH), 127.0 (CH), 114.8 (CH), 112.3 (CH_2), 62.4 (CH_2), 42.6 (CH_2). **(ESI) MS** calcd for $C_7H_9NNaO_2$ $[M+Na]^+$ 162.05 found 162.18.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-4-methyl-*N*-phenylbenzenesulfonamide (10f): Representative procedure **C** was followed using **9f** (59.2 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5)

yielded **10f** (20.4 mg, 34%) as a yellow solid. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.62. **M. p.** = 97.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.43 – 7.37 (m, 3H), 7.32-7.26 (m, 3H), 7.01-6.99 (m, 2H), 6.32 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.03 (dd, *J* = 13.5, 11.1 Hz, 1H), 4.86 (dd, *J* = 13.5, 6.8 Hz, 2H), 2.46 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.1 (C_q), 136.1 (C_q), 135.6 (C_q), 134.4 (CH), 132.5 (CH), 130.2 (CH), 129.7 (CH), 129.5 (CH), 129.2 (CH), 127.5 (CH), 113.8 (CH), 112.8 (CH_2), 21.6 (CH_3). **(ESI) MS** calcd for $C_{17}H_{18}NO_2S$ $[M+H]^+$ 300.11 found 300.20.

(*E*)-*N*-Benzyl-*N*-(buta-1,3-dien-1-yl)-4-methylbenzenesulfonamide (10g): Representative procedure **C** was followed using **9g** (939 mg, 3.0 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10g** (710 mg, 76%) as a tan orange solid. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.52. **M. p.** = 83.0 °C. **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.79 – 7.54 (m, 2H), 7.45 – 7.23 (m, 7H), 7.05 (d, *J* = 14.1 Hz, 1H), 6.28 (dt, *J* = 16.9, 10.4, 1H), 5.43 (dd, *J* = 14.0, 10.5 Hz, 1H), 4.94 (d, *J* = 16.9 Hz, 1H), 4.89 (d, *J* = 10.4 Hz, 1H), 4.60 (s, 2H), 2.49 (s, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 144.4 (C_q), 135.8 (C_q), 135.6 (C_q), 134.6 (CH), 130.0 (CH), 129.9 (CH), 128.6 (CH), 127.5 (CH), 126.9 (CH), 126.8 (CH), 113.6 (CH), 112.9 (CH_2), 49.3 (CH_2), 21.3 (CH_3). **(ESI) MS** calcd for $C_{18}H_{20}NO_2S$ $[M+H]^+$ 314.12 found 314.27.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-*N*-hexyl-4-methylbenzenesulfonamide (10h): Representative procedure **C** was followed using **9h** (76.8 mg, 0.25 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10h** (58.8 mg, 78%) as a yellow oil. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.58. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 14.1 Hz, 1H), 6.33 (dt, *J* = 16.9, 10.3 Hz, 1H), 5.48 (dd, *J* = 14.1, 10.5 Hz, 1H), 5.06 (d, *J* = 17.1 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 3.36 – 3.25

(m, 2H), 2.44 (s, 3H), 1.59 (dd, *J* = 14.0, 6.6 Hz, 2H), 1.34 – 1.26 (m, 6H), 0.99 – 0.80 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.8 (C_q), 136.2 (C_q), 135.0 (CH), 130.0 (CH), 129.8 (CH), 126.9 (CH), 113.4 (CH), 111.5 (CH_2), 45.7 (CH_2), 31.3 (CH_2), 27.0 (CH_2), 26.4 (CH_2), 22.5 (CH_2), 21.5 (CH_3), 14.0 (CH_3). **(ESI) MS** calcd for $C_{17}H_{26}NO_2S$ $[M+H]^+$ 308.17 found 308.25.

(*E*)-*N*-(buta-1,3-dien-1-yl)-4-methyl-*N*-(1-phenylethyl)benzenesulfonamide (10i): Representative procedure **C** was followed using **9i** (65.5 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 90:10) yielded **10i** (44.0 mg, 67%) as a yellow viscous oil. **R_f** *n*-hexanes/EtOAc 8:2 = 0.58. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.39 – 7.16 (m, 7H), 6.52 (d, *J* = 14.3 Hz, 1H), 6.14 (dt, *J* = 16.9, 10.3 Hz, 1H), 5.53 (dt, *J* = 14.0, 9.1 Hz, 2H), 4.98 – 4.75 (m, 2H), 2.47 (d, *J* = 7.8 Hz, 3H), 1.51 (t, *J* = 6.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.9 (C_q), 139.2 (C_q), 137.0 (C_q), 135.1 (CH), 129.8 (CH), 128.5 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 126.7 (CH), 117.5 (CH), 114.1 (CH_2), 55.6 (CH), 21.6 (CH_3), 16.1 (CH_3). **(ESI) MS** calcd for $C_{19}H_{21}NNaO_2S$ $[M+Na]^+$ 350.12 found 350.31.

(*R*)-(*E*)-*N*-(buta-1,3-dien-1-yl)-4-methyl-*N*-(1-phenylethyl)benzenesulfonamide (10i): Representative procedure **C** was followed using **(*R*)-9i** (65.5 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 9:1) yielded **(*R*)-10i** (48.2 mg, 74%, *ee* > 99%) as a yellow viscous oil.

***(E)*-*N*-(Buta-1,3-dien-1-yl)-N-(4-fluorobenzyl)-4-methylbenzenesulfonamide (10j):** Representative procedure **C** was followed using **9j** (66.3 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10j** (57.1 mg, 86%) as a viscous orange oil.

R_f *n*-hexanes/EtOAc 8:2 = 0.55. **^{1}H NMR** (400 MHz, Acetone-d_6) δ 7.79 (t, *J* = 7.9 Hz, 2H), 7.51 – 7.36 (m, 4H), 7.15 – 7.09 (m, 2H), 7.06 (d, *J* = 14.0 Hz, 1H), 6.32 (dt, *J* = 17.0, 10.3 Hz, 1H), 5.54 (dd, *J* = 14.0, 10.5 Hz, 1H), 4.90 (d, *J* = 17.0 Hz, 1H), 4.82 (d, *J* = 10.2 Hz, 1H), 4.65 (s, 2H), 2.46 (s, 3H). **^{13}C NMR** (101 MHz, Acetone-d_6) δ 162.1 (d, *J* = 246 Hz, C_q), 144.4 (C_q), 136.1 (C_q), 134.9 (CH), 132.2 (d, *J* = 3 Hz, C_q), 130.0 (CH), 129.8 (CH), 129.0 (d. *J* = 8 Hz, CH), 127.0 (CH), 115.2 (d, *J* = 22 Hz, CH), 113.3 (CH), 113.2 (CH_2), 48.3 (CH_2), 20.6 (CH_3). **^{19}F NMR** (376 MHz, Acetone-d_6) δ -116.7. **(ESI) MS** calcd for $C_{18}H_{19}FNO_2S$ $[M+H]^+$ 332.11 found 332.29.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-*N*-(3-chloro-4-fluorobenzyl)-4-methylbenzenesulfonamide (10k): Representative procedure **C** was followed using **9k** (91.2 mg, 0.25 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10k** (59.1 mg, 65%) as a yellow solid. **R_f** *n*-hexanes/EtOAc 8:2 = 0.56. **M. p.** = 101.7 °C. **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.30 (m, 2H), 7.33 – 7.31 (m, 1H), 7.17 – 7.14 (m, 1H), 7.12 – 7.05 (m, 1H), 7.03 (d, *J* = 14.1 Hz, 1H), 6.29 (dt, *J* = 16.9, 10.3 Hz, 1H), 5.43 – 5.33 (m, 1H), 4.97 (d, *J* = 16.9 Hz, 1H), 4.89 (d, *J* = 10.3 Hz, 1H), 4.54 (s, 2H), 2.47 (s, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 157.3 (d, *J* = 254 Hz, C_q), 144.7 (C_q), 135.6 (C_q), 134.4 (CH), 132.8 (CH), 130.0 (CH), 129.5 (d, *J* = 6 Hz, CH), 128.9 (CH), 126.8 (CH), 126.7 (d, *J* = 5 Hz, C_q), 121.1 (d, *J* = 18 Hz, C_q), 116.6 (d, *J* = 21 Hz, CH), 114.1 (CH), 113.0 (CH_2), 48.2 (CH_2), 21.3 (CH_3). **^{19}F NMR** (376 MHz, CD_2Cl_2) δ -118.0. **(ESI) MS** calcd for $C_{18}H_{18}ClFNO_2S$ $[M+H]^+$ 366.07 found 366.21.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-4-methyl-N-(naphthalen-1-ylmethyl)benzenesulfonamide (10l): Representative procedure **C** was followed using **9l** (90.8 mg, 0.25 mmol). Purification by column chromatography on silica

gel (*n*-hexanes/EtOAc 95:5) yielded **10l** (68.6 mg, 76%) as a pale orange solid. **R_f** *n*-hexanes/EtOAc 8:2 = 0.60. **M. p.** = 127.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.87 (m, 2H), 7.81 – 7.72 (m, 2H), 7.59 – 7.50 (m, 2H), 7.44 – 7.32 (m, 5H), 7.14 (d, *J* = 14.0 Hz, 1H), 6.26 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.31 (dd, *J* = 14.7, 9.8 Hz, 1H), 5.12 (s, 2H), 4.88 – 4.73 (m, 2H), 2.48 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.2 (C_q), 135.9 (C_q), 134.5 (CH), 133.7 (C_q), 130.3 (C_q), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.4 (C_q), 127.9 (CH), 127.1 (CH), 126.3 (CH), 125.7 (CH), 125.6 (CH), 124.1 (CH), 122.1 (CH) , 114.1 (CH), 113.2 (CH_2), 47.5 (CH_2), 21.6 (CH_3). **(ESI) MS** calcd for $C_{22}H_{21}KNO_2S$ $[M+K]^+$ 402.09 found 402.06.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-*N*-(2,4-dimethoxybenzyl)-4-methylbenzenesulfonamide (10m): Representative procedure **C** was followed using **9m** (74.6 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10m** (60.6 mg, 81%) as a yellowish solid. **R_f** *n*-hexanes/EtOAc 8:2 = 0.42. **M. p.** = 93.7 °C. **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.20 (dd, *J* = 13.8, 8.8 Hz, 1H), 7.03 (d, *J* = 14.0 Hz, 1H), 6.50 (dd, *J* = 5.3, 2.2 Hz, 2H), 6.30 (dt, *J* = 17.0, 10.4 Hz, 1H), 5.48 – 5.37 (m, 1H), 4.93 (d, *J* = 16.9 Hz, 1H), 4.88 (d, *J* = 10.3 Hz, 1H), 4.51 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.47 (s, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 160.4 (C_q), 157.5 (C_q), 144.2 (C_q), 136.0 (C_q), 134.9 (CH), 130.0 (CH), 129.9 (CH), 128.3 (CH), 126.8 (CH), 115.4 (C_q), 113.3 (CH), 112.4 (CH_2), 104.4 (CH), 98.1 (CH), 55.3 (CH_3), 55.3 (CH_3), 43.6 (CH_2), 21.3 (CH_3). **(ESI) MS** calcd for $C_{20}H_{23}KNO_4S$ $[M+K]^+$ 412.10 found 412.22.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-*N*-[2-(5-fluoro-1-methyl-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (10n): Representative procedure **C** was followed using **9n** (79.6 mg, 0.20 mmol) and PPh_3 (0.02 mmol, 5.2 mg). Purification by

column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **10n** (45.3 mg, 57%) as a yellowish oil. **R_f** *n*-hexanes/EtOAc 8:2 = 0.35. **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.73 – 7.67 (m, 2H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.29 – 7.23 (m, 2H), 7.03 (s, 1H), 7.02 – 6.95 (m, 2H), 6.48 – 6.32 (m, 1H), 5.70 – 5.58 (m, 1H), 5.15 – 5.06 (m, 1H), 5.02 – 4.94 (m, 1H), 3.76 (d, *J* = 3.5 Hz, 3H), 3.66 – 3.56 (m, 2H), 3.05 – 2.97 (m, 2H), 2.44 (s, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 157.6 (d, *J* = 234 Hz, C_q), 141.2 (C_q), 136.1 (C_q), 134.8 (CH), 133.7 (C_q), 129.9 (CH), 129.7 (CH), 128.7 (CH), 127.9 (d, *J* = 9Hz, C_q), 126.8 (CH), 113.3 (CH), 111.7 (CH_2), 110.6 (d, *J* = 5 Hz, C_q), 110.1 (d, *J* = 10 Hz, CH), 109.7 (d, *J* = 27 Hz, CH), 103.4 (d, *J* = 24 Hz, CH), 46.2 (CH_2), 32.8 (CH_3), 23.4 (CH_2), 21.2 (CH_3). **^{19}F NMR** (376 MHz, CD_2Cl_2) δ -126.1. **(ESI) MS** calcd for $C_{22}H_{23}KFN_2O_2S$ $[M+K]^+$ 437.11 found 437.19.

(*E*)-*N*-(Buta-1,3-dien-1-yl)-*N*-[2-(6-chloro-1-methyl-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (10o): Representative **C** procedure was followed using **9o** (41.4 mg, 0.10 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **10o** (25.2 mg, 61%) as a sticky orange oil. **R_f** *n*-hexanes/EtOAc 8:2 = 0.36. **^{1}H NMR** (300 MHz, CD_2Cl_2) δ 7.69 – 7.62 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.33-7.26 (m, 3H), 7.09 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.98 (d, *J* = 14.0 Hz, 1H), 6.92 (s, 1H), 6.37 (dd, *J* = 16.8, 10.4 Hz, 1H), 5.77 – 5.47 (m, 1H), 5.06 (d, *J* = 16.8 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 3.71 (s, 3H), 3.59 (dt, *J* = 13.2, 6.8 Hz, 2H), 3.03 (dd, *J* = 9.2, 6.6 Hz, 2H), 2.46 – 2.35 (m, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2) δ 144.2 (C_q), 137.4 (C_q), 136.1 (C_q), 134.8 (CH), 129.8 (CH), 129.7 (CH), 127.8 (C_q), 127.5 (CH), 126.7 (CH), 126.3 (C_q), 119.6 (CH), 119.4 (CH), 113.3 (CH), 111.6 (C_q), 111.0 (CH_2), 109.3 (CH), 46.3(CH_2), 32.6 (CH_3), 23.3 (CH_2), 21.2 (CH_3). **(ESI) MS** calcd for $C_{22}H_{24}ClN_2O_2S$ $[M+H]^+$ 415.13 found 415.28.

(*E*)-*N*-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-*N*-(buta-1,3-dien-1-yl)-4-methylbenzenesulfonamide (10p): Representative **C** procedure was followed using **9p** (78.8 mg, 0.20 mmol) and PPh_3 (0.02 mmol). Purification by column cchromatography on silica gel (*n*-hexanes/EtOAc 80:20) yielded **10p** (40.5 mg, 51%) as a white solid. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.15. **M. p. =** 125.8 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 2H), 7.38 – 7.21 (m, 8H), 6.89 (d, *J* = 13.9 Hz, 1H), 6.20 (dd, *J* = 17.3, 10.1 Hz, 1H), 5.68 (dd, *J* = 14.1, 10.5 Hz, 1H), 5.46 (s, 2H), 4.98 (d, *J* = 17.2 Hz, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.65 (s, 2H), 2.40 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.2 (C_q), 143.7 (C_q), 135.5 (C_q), 134.4 (C_q), 134.3 (CH), 129.9 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 127.9 (CH), 126.8 (CH), 122.7 (CH), 114.5 (CH), 112.8 (CH_2), 54.1 (CH_2), 41.6 (CH_2), 21.5 (CH_3). **(ESI) MS** calcd for $C_{21}H_{23}N_4O_2S$ $[M+H]^+$ 395.15 found 395.33.

***N*-[(*E*)-buta-1,3-dien-1-yl]-*N*-[(*E*)-3,7-dimethylocta-2,6-dien-1-yl]-4-methylbenzenesulfonamide (10q):** Representative **C** procedure was followed using **9q** (71.8 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 98:2) yielded **10q** (43.4 mg, 60%) as a yellow oil. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.71. **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.67 (t, *J* = 6.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.96 (dd, *J* = 14.0, 4.7 Hz, 1H), 6.34 (dt, *J* = 16.9, 10.4 Hz, 1H), 5.49 (dd, *J* = 14.0, 10.5 Hz, 1H), 5.09 – 4.99 (m, 2H), 4.93 (dd, *J* = 11.3, 5.2 Hz, 2H), 4.08 (t, *J* = 7.5 Hz, 2H), 2.45 (s, 3H), 1.95 (tt, *J* = 26.7, 13.5 Hz, 4H), 1.74 – 1.63 (m, 6H), 1.61 – 1.53 (m, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 144.1 (C_q), 139.2 (C_q), 136.5 (C_q), 135.0 (CH), 131.6 (C_q), 130.0 (CH), 129.7 (CH), 126.9 (CH), 123.7 (CH), 118.2 (CH), 113.1 (CH), 112.0 (CH_2), 44.1 (CH_2), 39.2 (CH_2), 26.1 (CH_2), 25.3 (CH_3), 21.2 (CH_3), 17.3 (CH_3), 16.1 (CH_3). **(ESI) MS** calcd for $C_{21}H_{29}KNO_2S$ $[M+K]^+$ 398.16 found 398.26.

***N*-Benzyl-4-methyl-*N*-[(*1E*,*3E*)-penta-1,3-dien-1-yl]benzenesulfonamide (10s):** Representative procedure **C** was followed using **9s** (65.4 mg, 0.20 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10s** (41.3 mg, 63% as a mixture *E*,*E* :*E*,*Z* = 3.2:1) as a yellow oil. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.64. **^{1}H NMR** (400 MHz, $CDCl_3$, major isomer) δ 7.77 – 7.67 (m, 2H), 7.39 – 7.22 (m, 7H), 6.86 (d, *J* = 14.0 Hz, 1H), 6.01 – 5.83 (m, 1H), 5.47 – 5.32 (m, 2H), 4.52 (s, 2H), 2.46 (s, 3H), 1.69 (dd, *J* = 6.8, 1.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$, major isomer) δ 143.9 (C_q), 136.0 (C_q), 135.6 (C_q), 129.9 (CH), 128.8 (CH), 128.6 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 126.4 (CH), 113.4 (CH), 49.51 (CH_2), 21.6 (CH_3), 18.1 (CH_3). **(ESI) MS** calcd for $C_{19}H_{21}KNO_2S$ $[M+K]^+$ 366.09 found 366.52.

***N*-Benzyl-*N*-[(*1E,3E*)-hepta-1,3-dien-1-yl]-4-methylbenzenesulfonamide (10t):** Representative procedure **C** was followed using **9t** (88.8 mg, 0.25 mmol). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 95:5) yielded **10t** (48.0 mg, 54% as a mixture *E*,*E* :*E*,*Z* = 4.0:1) as a yellow oil. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.55. **^{1}H NMR** (400 MHz, CD_2Cl_2, major isomer) δ 7.74 – 7.70 (m, 2H), 7.41 – 7.29 (m, 7H), 6.87 (d, *J* = 14.0 Hz, 1H), 6.03 – 5.89 (m, 1H), 5.47 – 5.38 (m, 2H), 4.56 (s, 2H), 2.48 (s, 3H), 2.08 – 1.91 (m, 2H), 1.41 – 1.22 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2, major isomer) δ 144.2 (C_q), 136.9 (C_q), 136.8 (C_q), 131.9 (CH), 129.9 (CH), 128.6 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 113.3 (CH), 49.4 (CH_2), 34.7 (CH_2), 29.6 (CH_2), 22.6 (CH_2), 21.3 (CH_3), 13.4 (CH_3). **(ESI) MS** calcd for $C_{21}H_{26}NO_2S$ $[M+H]^+$ 356.17 found 356.36.

4-Methyl-*N*-(4-methylbenzyl)-*N*-[(*1E*,*3E*,*5E*)-6-phenylhexa-1,3,5-trien-1-yl]benzenesulfonamide (10r): Representative procedure **C** was followed using **9r** (85.8 mg, 0.20 mmol). Purification by column chromatography on silica gel

(*n*-hexanes/EtOAc 95:5) yielded **10r** (56.8 mg, 66% as a mixture *E,E,E* : *E,Z,E* = 6.6:1) as an orange viscous oil. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.48. **^{1}H NMR** (400 MHz, CD_2Cl_2, major isomer) δ 7.79 – 7.70 (m, 2H), 7.42 – 7.37 (m, 4H), 7.35-7.30 (m, 3H), 7.25-7.17 (m, 4H), 7.08 (d, *J* = 14.8 Hz, 1H), 6.82 (dd, *J* = 15.5, 10.6 Hz, 1H), 6.45 (d, *J* = 15.5 Hz, 1H), 6.32 (dd, *J* = 14.8, 10.6 Hz, 1H), 6.16 (dd, *J* = 14.8, 10.6 Hz, 1H), 5.52 (dt, *J* = 18.4, 9.2 Hz, 1H), 4.56 (d, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.35 (s, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2, major isomer) δ 144.4 (C_q), 137.6 (C_q), 137.4 (C_q), 135.8 (C_q), 132.4 (C_q), 131.3 (CH), 130.6 (CH), 130.0 (CH), 129.9 (CH), 129.8 (CH), 129.3 (CH), 129.1 (CH), 128.6 (CH), 127.2 (CH), 126.9 (CH), 126.8 (CH), 126.1 (CH), 112.7 (CH), 49.2 (CH_2), 21.3 (CH_3), 20.8 (CH_3). **(ESI) MS** calcd for $C_{27}H_{27}KNO_2S$ $[M+K]^+$ 468.14 found 468.28.

(*E*)-*N*-Benzyl-*N*-(hexa-3,5-dien-2-yl)-4-methylbenzenesulfonamide (10w'): Representative procedure **C** was followed using **9w** (68.3 mg, 0.20 mmol), $Pd(PPh_3)_4$ (10 mol %) and PCy_3 (20 mol %). Purification by column chromatography on silica gel (*n*-hexanes/EtOAc 98:2) yielded **10w'** (37.3 mg, 55%) as a yellow oil. $\mathbf{R_f}$ *n*-hexanes/EtOAc 8:2 = 0.63. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.68 (m, 2H), 7.45 – 7.12 (m, 7H), 6.13 (dt, *J* = 16.9, 10.2 Hz, 1H), 5.89 (dt, *J* = 10.4, 8.4 Hz, 1H), 5.38 (dd, *J* = 15.5, 5.8 Hz, 1H), 5.11 (t, *J* = 11.6 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 4.61 (p, *J* = 6.3 Hz, 1H), 4.50 (d, *J* = 15.8 Hz, 1H), 4.23 (d, *J* = 15.9 Hz, 1H), 2.61 – 2.33 (m, 3H), 1.14 (dd, *J* = 11.1, 8.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1 (C_q), 138.4 (C_q), 138.1 (C_q), 136.0 (CH), 132.8 (CH), 132.8 (CH), 129.6 (CH), 128.3 (CH), 128.0 (CH), 127.3 (CH), 127.2 (CH), 117.9 (CH_2), 54.8 (CH_2), 47.8 (CH), 21.5 (CH_3), 18.8 (CH_3). **(ESI) MS** calcd for $C_{20}H_{23}NNaO_2S$ $[M+Na]^+$ 364.13 found 364.02.

***N*-(1,3-dioxo-1,3,3*a*,4,7,7*a*-hexahydroisobenzofuran-4-yl)-4-methyl-*N*-(4-methylbenzyl)benzenesulfonamide (10aa):** In an oven-dried tube, **10a** (98.1 mg, 0.30 mmol) and maleic anhydride (44.1 mg, 0.45 mmol) were added sequentially and purged with nitrogen three times. Subsequently, toluene (2.0 ml) was added and the tube placed in a pre-heated oil bath at 100 °C. After completion (16 hs), the reaction mixture was cooled down at room temperature and CH_2Cl_2 (10 ml) was added. The mixture was concentrated under reduced pressure and the crude purified by column chromatography on silica gel (*n*-hexanes/EtOAc 9:1 → 6:4) to deliver **10aa** (84.4 mg, 64%) as a yellow solid. **M. p.** = 194.1 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.55 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.12 – 6.99 (m, 4H), 5.87 – 5.67 (m, 1H), 5.19 (d, J = 10.2 Hz, 1H), 4.93 (s, 1H), 4.51 (d, J = 16.6 Hz, 1H), 4.17 (d, J = 16.6 Hz, 1H), 3.39 (dd, J = 5.6, 4.0 Hz, 1H), 3.13 – 2.93 (m, 1H), 2.49 – 2.41 (m, 1H), 2.39 (d, J = 9.5 Hz, 3H), 2.27 (s, 3H), 2.14 (s, 1H). **^{13}C NMR** (101 MHz, DMSO) δ 174.2 (C_q), 173.0 (C_q), 143.4 (C_q), 137.8 (C_q), 136.1 (CH), 136.0 (C_q), 130.7 (CH), 129.9 (CH), 128.9 (CH), 127.8 (CH), 127.4 (CH), 124.1 (C_q), 57.8 (CH_2), 49.5 (CH), 44.6 (CH), 41.0 (CH), 24.4 (CH_2), 21.4 (CH_3), 21.1 (CH_3). **(ESI) MS** calcd for $C_{48}H_{53}N_4O_{10}S_2$ $[2M+NH_4+CH_3CN]^+$ 909.32 found 909.61.

One pot procedure: In an oven dried tube, **9a** (98.1 mg, 0.30 mmol), $Pd(PPh_3)_4$ (0.015 mmol), PPh_3 (0.03 mmol) and BzOH (0.09 mmol) were added sequentially and purged with nitrogen three times. Subsequently, toluene (2.0 ml, 0.1 M) was added under N_2 atmosphere and the tube placed in a pre-heated oil bath at 100 °C. After 16 hs, maleic anhydride (44.1 mg, 0.45 mmol) was added and the reaction mixture further stirred for 24 hs. After completion, the tube was cooled down at room temperature and CH_2Cl_2 (10 ml) was added. The mixture was concentrated under reduced pressure and the crude purified by

chromatography on silica gel (*n*-hexanes/EtOAc 9:1 → 6:4) to deliver **10aa** (75.2 mg, 57%) as a yellow solid.

4.5 References

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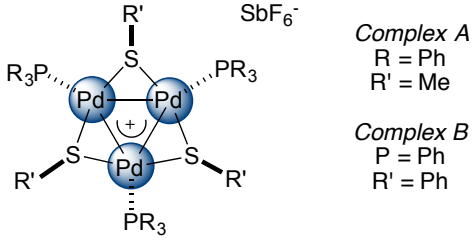
5 Trinuclear Palladium Clusters Catalysis

From this chapter: *ACS Catal*. **2018**, *8*, 144−147; Matteo Lanzi, Tatiana Cañeque, Luciano Marchio', Raimondo Maggi, Franca Bigi, Max Malacria, Giovanni Maestri

5.1 Introduction

As discussed in the introduction, cycloisomerizations are prototypical sustainable reactions that have been intensely studied exploiting mononuclear transition metal catalysts. [180–183] Predominantly, soft π-acidic noble-metal complexes such as gold and platinum ones were used. [68,184–186] A class of cycloisomerization reactions is the polycyclization of polyunsaturated substrates. This is of special interest for the synthesis of natural products. Pivoting on the high activity of tripalladium complexes in the semireduction of internal akynes, we wondered whether it would have been possible to develope C−C bond forming cascades via alkyne actiavation using Pd_3^+ complexes. To the best of our knowledge, no discrete palladium cluster has been able yet to induce the selective formation of C−C bonds from unsaturated reagents. Herein, we report the reactivity of either terminal enynes and internal dienynes with all-metal aromatic Pd_3^+ complexes.

5.2 Results and discussion



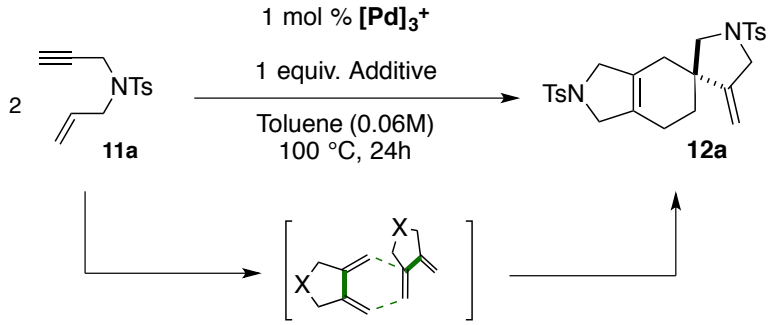
Scheme 32: $[Pd]_3^+$ Clusters

We started using 1,6-enyne (**11a**) with 1 mol % of Pd_3^+ in a dry and degassed solvent. The solution was then warmed and samples were periodically taken to monitor the reaction by TLC. Upon screening a variety of conditions, we never observed the least trace of conversion. However, the addition of triethylammonium formate (2 equiv) gave a proof of principle of the feasibility of our approach. Full conversion of **11a** was observed upon 6 h. This result suggested that a Brønsted acid was required in combination with the metal complex to activate the triple bond, in analogy to conditions used for alkyne semireductions under transfer hydrogenation conditions.

The main product was the linear diene coming from reduction of **11a** (35%) and broad ^{13}C NMR peaks suggested that partial polymerization occurred, despite a dilute reaction mixture (0.06 M).

However, we were intrigued by the appearance of nuclear magnetic resonance (NMR) resonances different from those of literature precedents. Isolation and characterization of the product (**12a**, 21%) revealed that a formal enyne dimerization occurred, enabling the assembly of three fused cycles through the creation of four new C−C bonds. The central ring of **12a** had a hindered tetra-substituted double bond and a spiro carbon. Use of 1 equiv of triethylammonium formate gave a small improvement. No conversion was observed by replacing ammonium formate with trimethylamine, which rules out the requirement of the

base.

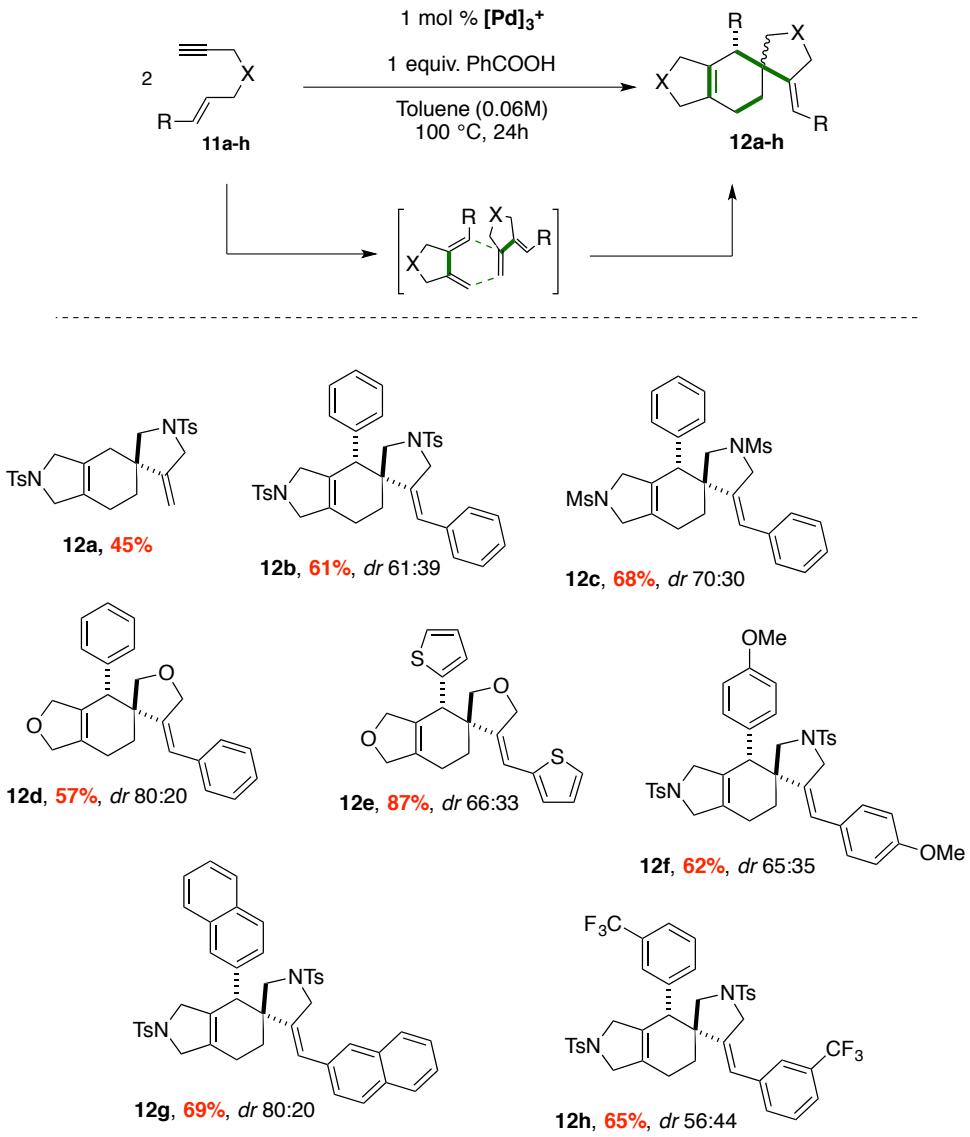


Entry[a]	Additive	Yield of 12a [%]
1	$Et_3NHCOOH$	21
2	$Et_3NHCOOH$	27
3	Et_3N	
4	HCOOH	35
5	C_6H_5OH	24
6	TsOH	
7	AcOH	45
8	PhCOOH	45
9	PhCOOH	42
10	PhCOOH	

[a]Conditions: **11a** (0.3 mmol, 0.06 M), $[Pd]_3^+$ (1 mol %), 1 equiv of additive, N2, 6 h, 100 °C.; [b] Isolated yields; [c] 2 equiv.; [d] 2 equiv, 36 h; [e] without A.

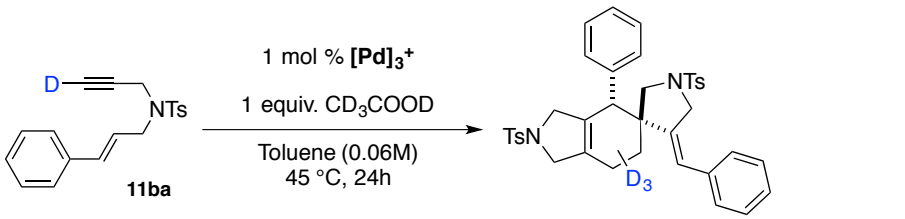
The yield slightly increased with formic acid. Phenol provided **12a** in 24% yield. Extensive decomposition occurred with 1 equiv of PTSA. The best compromise to minimize side reactions was achieved with either acetic or benzoic acid. The reaction is slower with 0.2 equiv of acid. These results showed the requirement of a mildly acidic environment to trigger these reactions. Product **12a** did not

form without complex **A**. **12a** did not form under these conditions using either $Pd(OAc)_2$ or $Pd(dba)_2$. These data suggest that the formal enyne dimerization is a peculiar feature of the all-metal aromatic trinuclear complex. Therefore, we checked the generality of this method.



Scheme 33: Scope of *E*-alkenes

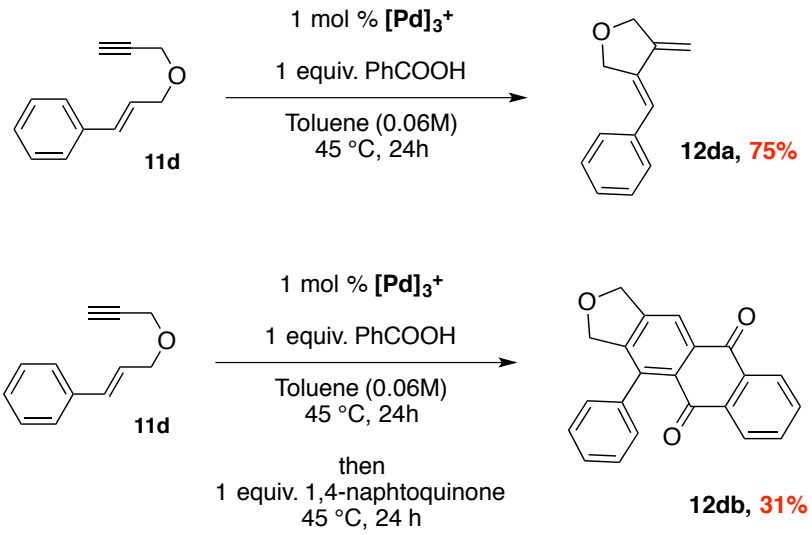
A substituted olefin proved beneficial and provided **12b** in 61% yield as a 61:39 mixture of diastereoisomers. Their relative configuration has been assigned through NMR correlation experiments. Mesyl chloride as a protecting group was well tolerated leading to a comparable yield (68%). The diastereoselection was slightly higher in this case (dr = 80:20). Replacement of the nitrogen tether with an oxygen one is tolerated. The phenyl substituent could be replaced by hetero-cycles, such as 2-thienyl units. This proved beneficial for yield. Similarly, both electron withdrawing and donating groups are well tolerated. No other isomers of **12** were observed, neither by NMR nor via mass spectrometry (MS) analyses. In order to study the reaction mechanism, we performed deuterium labelling experiments, starting with the preparation of the deuterated substrate **11ba**. We conducted the reaction in deuterated acetic acid, obtaining the desired product with a good yield and diastereomeric ratio (77%, *dr* = 63:37). The ^{1}H and ^{2}D NMR spectra showed the incorporation of deuterium and ESI-MS analysis showed a mixture of deuterated species. In particular, the most abundant species was the tri deuterated product. This implies that a proton/deuterium exchange takes place during the catalytic cycle. Further computational studies will be however require to fully rationalize the mechanism of the whole sequence.



Scheme 34: Deuterated experiments with **11ba**

Reagrding the formal dimerization, we reasoned that this might have been due to a 4 + 2 cyclization between two monocyclic 1,3-dienes, which would favor the

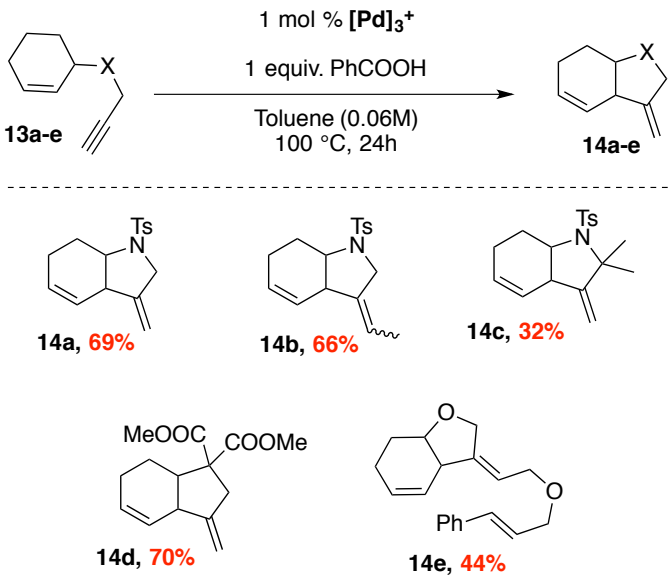
formation of a single regioisomer thanks to secondary orbital interactions. [187–189] We performed the reaction on enyne **1c** at 45 °C to confirm this hypothesis.



Scheme 35: Cycloisomerization of **11d** and further applicability of **12da** in Diels-Alder reaction

This enabled to identify 1,3-diene (**12da**) in 75% yield, pointing toward a Diels−Alder cyclization at the root of the cascade leading to **12**. Pivoting on the electron-rich nature of diene **12da**, we tried to quench it with an electron-poor dienophile. The addition of an oxygen balloon promoted the rearomatization of the intermediate cyclohexene and enabled to recover fused tetracyclic quinone **12db** in 31% yield after 48 at 45 °C. [190] Try as we might, we were so far unable to improve this yield, although the multistep assembly of decorated polycyclic anthraquinones is often much more worrisome. [191] Taken together, these results suggest that the Pd_3^+ catalyst can trigger the formation of conjugated exocyclic dienes from terminal enynes and their sequential Diels−Alder cycloaddition to form tricycles **12**.

We then tested *Z*–alkenes by preparing enynes **13**. Under optimized conditions, we could isolate 1,4-dienes **14** as single diastereomers. The complete selectivity to 1,4-dienes was observed by Trost using similar reagents. [67,192]



Scheme 36: Scope of Z-alkenes

We then switched to internal triple bonds by preparing dienynes **15**. Optimization of conditions showed that best results are obtained in chloroform at 45 °C with either acetic or benzoic acid at a 0.6 M concentration. Symmetric reagents (**15a-d**) delivered the corresponding tricycles (**16a-d**) with very high diastereocontrol (up to 98:2) and good to excellent yields (up to 87 %). The relative configuration of the four contiguous stereocenters of the central cyclohexene ring was established via X-ray analyses on **16b**.

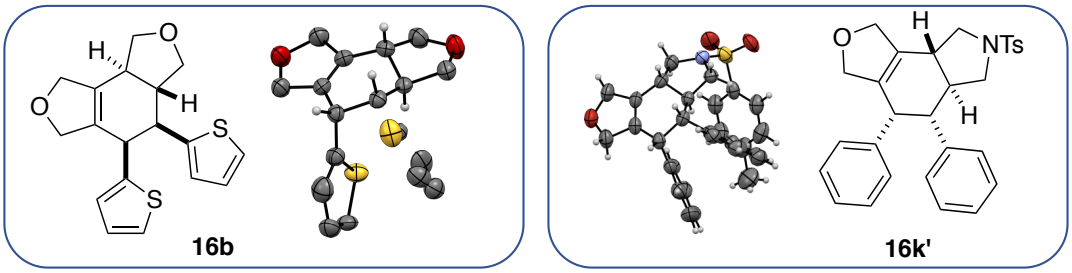
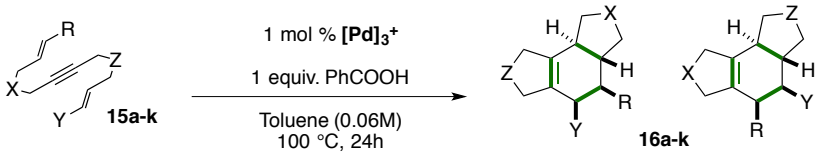
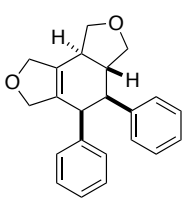


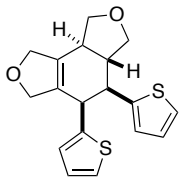
Figure 8: Single Cristal X-Ray diffraction of **16b** and **16k'**

Unexpected results came varying alkene fragments. The dienyne with one phenyl and one thienyl ring delivered a 6:4 mixture of tricycles **16e** and **16e'**, in which the relative position of these two aromatics on the central ring is scrambled (58% combined yield). Both products were formed with excellent diastereocontrol (92:8). The same trend was observed with a phenyl and an anisole fragment, **16f** and **16f'** forming in a 1:1 ratio. They both displayed almost complete diastereoselection (97:3, 51% yield). We functionalized the dienyne with an aromatic and an ester unit to test electronic effects. The reaction afforded **16g** and **16g'** in a 1:1 mixture (67% yield, *dr* = 98:2). A slight difference is observed with an ester combined with a thiophene, **16h** and **16h'** being recovered in a 3:1 mixture. The diastereomeric ratio of **16h** is 97:3 (a minor isomer of **16h'** was not detected). Remarkably, this trend is observed with a sterically demanding gem-dimethyl substituent alpha to the triple bond. Products **16i** and **16i'** were retrieved in 6:4 ratio and 87% combined yield. Once again, diastereoselectivity was very high for both tricycles (94:6). A malonate tether followed suit, enabling one to access hidrindane motifs (**16j** and **16j'** in a 1:1 ratio, *dr* = 93:7, 61% yield). The method allows to access nitrogen heterocycles, as portrayed by **16k** and **16k'**, which evenly formed in 82% combined yield (*dr* = 88:12). X-ray analysis on the latter paralleled the result of **16k'**. Formation of **16i** − **16k** required to heat the reaction mixture at 70 °C.

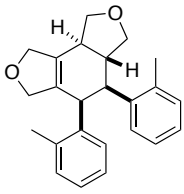




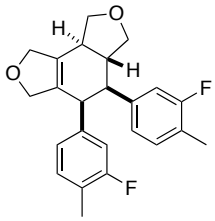
16a, 87%, *dr* 93:7



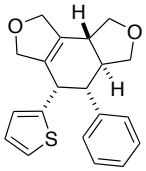
16b, 65%, *dr* 96:4

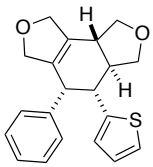


16c, 62%, *dr* 98:2

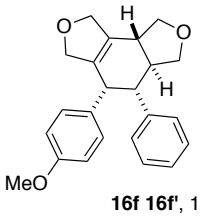


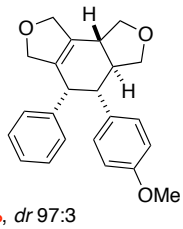
16d, 65%, *dr* 98:2



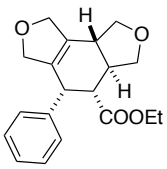


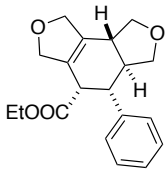
16e 16e', 6:4, 58%, *dr* 92:8



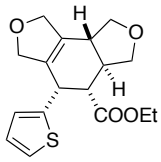


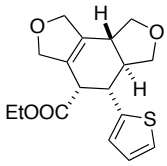
16f 16f', 1:1, 51%, *dr* 97:3



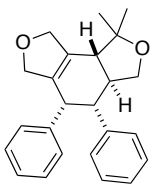


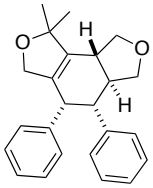
16g 16g', 1:1, 67%, *dr* 98:2



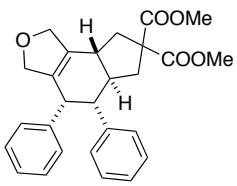


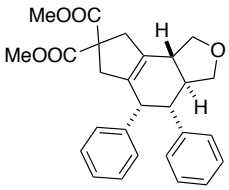
16h 16h', 3:1, 70%, *dr* 93:7



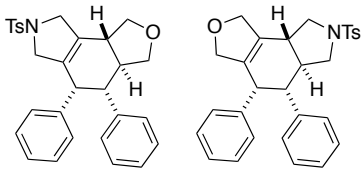


16i 16i', 6:4, 87%, *dr* 96:4





16j 16j', 1:1, 61%, *dr* 93:7



16k 16k', 1:1, 82%, *dr* 88:12

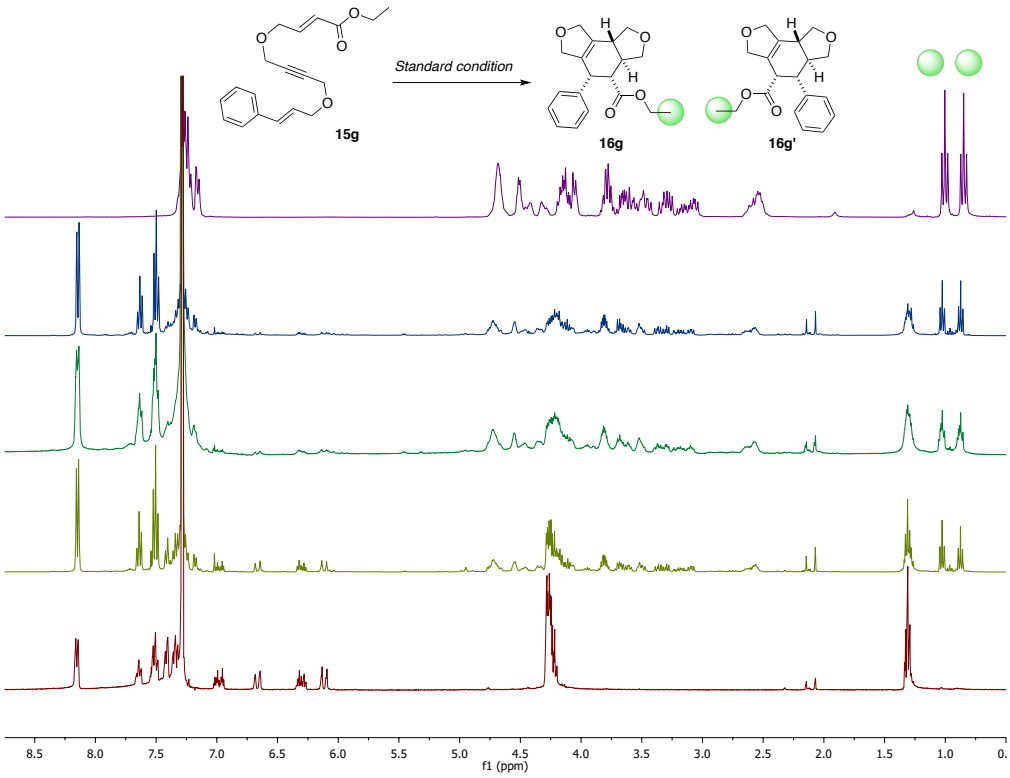
Scheme 37: Scope of dienynes

According to density functional theory (DFT), formic acid can interact with the delocalized HOMO of the prototypical subnanometric metal surface (ΔH = −11.5, −13.5, and −14.1 kcal/mol with PMe_3, PPh_3, and $P(tolyl)_3$, respectively, as ligands). This suggests that the core of Pd_3^+ complex **A** has basic character despite its positive charge. [179] Entropy factors are disfavorable (ΔG = +2.7, −1.5, and −1.4 kcal/mol, respectively), correlating with NMR observations. This fits with the effect of acid concentration on rate and suggests that the actual concentration of acid adducts always remains tiny, contributing to the chemical stability of **A** itself. Analyses of the ^{31}P spectra indeed showed the diagnostic resonance of complex **A** throughout the reaction. Similar chemical stabilities are usually not observed with mononuclear Pd, Pt, and Au complexes instead. This correlates with MS and ultraviolet−visible light (UV-vis) analyses on alkyne semireductions and suggests that **A** is actually the catalyst of present cascade. This is confirmed by modeling, with the formation of various Pd(n) monomeric and dimeric complexes from Pd_3^+ being highly endoergonic.

Products **16** are complementary to reported polycyclization of dienynes. [193–196] In all cases presented, the diastereocontrol is very high. The relative configuration of the four contiguous stereocenters of **16** is always identical, regardless of either steric factors (**16i**) or electronic factors (**16g** and **16h**). This is at odds with an initial electrophilic alkyne activation, followed by nucleophilic olefin attack to form an intermediate 1,3-diene. As an alternative route, Brønsted acids can trigger the formation of Pd(II) hydrides from the corresponding Pd(0) complexes. This leads to alkyne hydrometalation, followed by alkene insertion into the resulting Pd−C bond. Products are eventually released via *β*-hydride elimination. We performed the reaction with deuterated acetic acid to test this possibility. No deuterium incorporation in **16a** has been observed by ^1H NMR and MS analyses. Taken together, these observations seem to exclude the

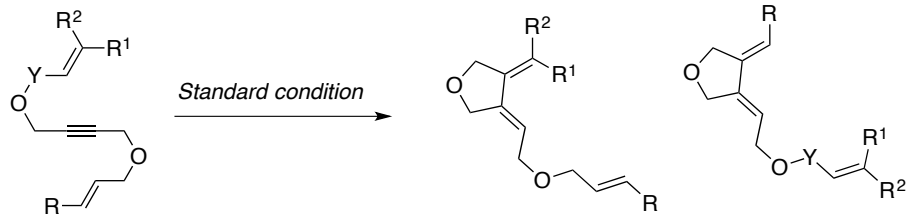
involvement of Pd hydrides, in contrast to observation made using 1,6-enynes instead. [175] A complementary mechanism involves the oxidative cycloaddition of a linear enyne on Pd(II) to provide the corresponding bicyclic Pd(IV) metallacycle. A diene can be released through sequential β-hydride and C−H reductive eliminations. A similar pathway seems to be the most likely, **16** and **16′** products stemming from alkene competition on the formation of an intermediate metallacycle.

We then monitored the reaction of **15g** by NMR. The reagent converts directly to **16g** and **16′g**. No intermediate triene resonances are observed in the vinyl region throughout the reaction.



Scheme 38: ^{1}HNMR monitoring reaction of 15g

In contrast, traces of triene resonances are observed by monitoring the reaction of **15a**, which did not have an electron-poor alkene group. In these cases, monocyclic trienes with a conjugated 1,3-diene motif are retrieved.



A R = H, R^1 = H, R^2 = H, Y = CH_2 **81%**
B R = H, R^1 = Ph, R^2 = H, Y = CH_2 **52%** (1:1)
C R = Ph, R^1 = CH_3, R^2 = CH_3, Y = CH_2 **45%** (1:1)
D R = Ph, R^1 = Ph, R^2 = H, Y = CO **54%** (0:1)

Scheme 39: Triene products

These findings suggest that the formation of **16** is eventually due to a highly diastereoselective Diels−Alder cyclization, which became apparent by increasing the highest occupied molecular orbital (HOMO)−lowest unoccupied molecular orbital (LUMO) gap of substrates.

5.3 Conclusion

We introduced Pd_3^+ complexes in the synthesis of highly decorated tricycles from linear unsaturated reagents. These reactions provided interesting structural architectures, casting a bright light for future applications of all-metal aromatics in C− C bond-forming sequences.

5.4 Experimental section

General procedure for the synthesis of allyl acetate: To a mixture of $Pd(OAc)_2$ (5 mol %) and Ag_2CO_3 (0.6 equiv.) in benzene (0.1 M) were added the desiderate halide (8 mmol, 1 equiv.) and allylic acetate (16 mmol, 2 mmol). The resulting mixture was refluxed until complete conversion (monitored by TLC, from 3 to 6 hours). After celite filtration, the residue was carefully purified by flash chromatography.

General procedure for the synthesis of 1,6-enynes GP-1: To the solution of allyl acetate derivatives (1 equiv.) in CH_3OH (0.78 M) was added KOH (1.5 equiv.). The mixture was stirred and heated at 55 °C, the conversion was followed analyzing samples via TLC (ca. 2 h). Upon complete conversion of the substrate, the solution was diluted with DCM and washed with H_2O. The crude allyl alcohol was used without further purification. To the solution of allyl alcohol (1.1 equiv.) in THF dry (0.3M) was added PPh_3 (1.5 equiv.) and 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1 equiv.). The mixture was cooled to 0 °C and DIAD (1.5 equiv.) was added dropwise. The resulting mixture was stirred at room temperature until complete conversion monitored by TLC. Upon complete conversion of the substrate, the solution was carefully concentrated and purified by flash chromatography yielding the desiderate product.

General procedure for the synthesis of symmetric dienynes GP-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 desiderate allyl acetate (1.1 equiv.) and $Pd(PPh_3)_4$ (10 mol %) were then added. The reaction was stirred until complete

conversion (monitored by TLC, 16 hours). The mixture was then concentrated and carefully purified by flash chromatography to yield symmetric dienynes.

General procedure for the synthesis of asymmetric dienynes GP-3: To a solution of but-2-yne-1,4-diol (4 equiv.) in dry THF (0.5 M) was added dropwise Et_2Zn (2 equiv., 1 M in hexane). Then the desiderate allyl acetate (1 equiv.) and $Pd(PPh_3)_4$ (5 mol %) were then added. The reaction was stirred until complete conversion (monitored by TLC, 16 hours). The mixture was then concentrated and carefully purified by flash chromatography to yield the corresponding enynol. To a solution of desiderate enynol (1 equiv.) in dry THF/DMF (3:1, 0.6M) at 0 °C NaH (1.1 equiv., 60 % in paraffin oil) was dropwise added. The resulting mixture was stirred for 30 min. Cinnamyl chloride (1.2 equiv.) was then added at 0 °C. The reaction was stirred upon complete conversion, then was quenched with water and diluted with diethylether (1 mL). The organic phase was washed with a saturated solution of NaCl, dried over MgSO4 and concentrated under reduced pressure. The crude oil was eventually purified by flash column chromatography.

General procedure for the synthesis of clusters $[Pd]_3^+$ GP-4: $Pd(dba)_2$ (115 mg, 0.2 mmol, 1 equiv.) was dissolved in degassed $CHCl_3$ (20 mL). Triphenylphosphine (52.5 mg, 0.2 mmol, 1 equiv.) and dimethyldisulfide (9 μL, 0.1 mmol, 0.5 equiv.) or diphenyldisulfide (22.8 mg, 0.105 mmol, 0.5 equiv.) were then sequentially added under argon. The solution was kept under stirring for 3 hours and silver hexafluoroantimonate (24.11 mg, 0.0702 mmol) was then added under an argon flow. Stirring was maintained for 1 hour. The solution was filtered over celite and the solvent was evaporated in vacuo. The brown solid was washed with hexane until complete removal of free dba (3 x 20 mL). The cluster is then dried in vacuo (red powder) and further purified through crystallization

(hexane/$CHCl_3$ vapour diffusion).

General Procedure for the catalytic synthesis of 2 from 1,6-enynes GP-5: Complex **A** (5.0 mg, 0.0031 mmol, 1 mol%) and freshly degassed toluene (5 mL) are added under argon to a Schlenk-type flask. The desired substrate **1** (0.3 mmol, 0.06 M) and benzoic acid or acetic acid (0.3 mmol, 1 equiv.) were sequentially added. The mixture was heated at 100 °C and the conversion was followed analyzing sampes via TLC. Upon complete conversion of the substrate, the solution was diluted with 5 mL of DCM and purified by flash chromatography on silica gel.

General Procedure for the catalytic synthesis of 6 from dienynes GP-6: Complex **A** (2.5 mg, 1.68 μmmol, 1 mol%) was added under nitrogen to a solution of the desired substrate **5** (0.168 mmol, 1 equiv.) and benzoic acid (20.6 mg, 0.168 mmol, 1 equiv.) in freshly degassed dry $CHCl_3$ (280 μL, 0.05M). The mixture was heated at 45 (for **5a-f**) or 70 °C (for **5g-j**) and the conversion was followed analyzing sampes via TLC. Upon complete conversion of the substrate, the solution was diluted with 2 mL of DCM and purified by flash chromatography on silica gel.

***N*-allyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 11a**. This compound was prepared following literature procedure. White solid. Yield: 77% (1.88 g). Eluent: hexane/ethyl acetate 8:2. **^{1}H NMR** (300 MHz, $CDCl_3$): 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). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.5 (Cq), 135.9 (Cq), 131.8 (2CH), 129.5 (2CH), 127.7 (CH), 120.0 (CH2), 76.5 (Cq), 73.7 (CH), 49.0 (CH_2), 37.7 (CH_2), 21.5 (CH_3).

***N*-cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 11b**. This compound was prepared following literature procedure. White solid. Yield 90% (1.868 g). Eluent: hexane/ethyl acetate 9:1. **^{1}H NMR** (300 MHz, $CDCl_3$) 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). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.6 (Cq), 136.1 (Cq), 136.1 (Cq), 134.9 (CH), 129.5 (2CH), 128.6 (2CH), 128.1 (2CH), 127.8 (2CH), 126.5 (CH), 122.9 (CH), 76.6 (Cq), 73.9 (CH), 48.6 (CH_2), 35.9 (CH_2), 21.6 (CH_3).

***N*-cinnamyl-*N*-(prop-2-yn-1-yl)methanesulfonamide 11c**. White solid. 92 %, (4.4 g). To a solution of propargyl amina (1.29 mL, 20 mmol, 1 equiv.) and TEA (3.1 mL, 22.2 mmol, 1.11 equiv.) in dry DCM (35 mL, 0.6 M) at 0 °C was dropwise added MsCl (1.71 mL, 22 mmol, 1.1 equiv.). The reaction was kept under stirring at room temperature overnight. The mixture was deluded with AcOEt and washed with water, dried over Na_2SO_4 concentrated and carefully purified by flash chromatography yielding *N*-(prop-2-yn-1-yl)methanesulfonamide (2.55 g, 96 %, 19.1 mmol). To the solution of *N*-(prop-2-yn-1-yl)methanesulfonamide (2.55 g, 19.1 mmol, 1 equiv.), K2CO3 (3.2 g, 23 mmol, 1.2 equiv.) in dry acetone (30 mL, 0.6 M) was added dropwise cinnamyl chloride (2.95 mL, 21 mmol, 1.1 equiv.). The mixture was refluxed overnight. Then the mixture was concentrated and carefully purified by flash chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.8, 6.8 Hz, 2H), 4.11 (d, *J* = 2.5 Hz, 3H), 4.06 (dd, *J* = 6.8, 1.3 Hz, 3H), 2.99 (s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.9 (Cq), 135.0 (CH), 128.6 (2CH), 128.1 (CH), 126.5 (2CH), 122.7 (CH), 77.3 (Cq), 74.4 (Cq), 48.7 (CH_2), 38.4 (CH_3), 35.7 (CH_2).

(E)-(3-(prop-2-yn-1-yloxy)prop-1-en-1-yl)benzene 11d. This compound was prepared following literature procedure. Colourless oil. Yield: 52% (1.34 g). Eluent: diethylether/pentane 1:9. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.25 (m, 5H), 6.66 (dt, *J* = 15.9, 1.43 Hz, 1H), 6.29 (dtd, *J* = 15.9, 6.27, 0.5 Hz, 1H), 4.26 (dd, *J* = 6.20, 1.4 Hz, 2H), 4.22 (d *J* = 2.37, 0.5 Hz, 2H), 2.48 (dt, *J* = 2.38, 0.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 136.5 (Cq), 133.3 (CH), 128.5 (2CH), 127.8 (2CH), 126.5 (CH), 125.0 (CH), 79.7 (Cq), 74.5 (CH), 70.1 (CH_2), 57.0 (CH_2).

(*E*)-2-(3-(prop-2-yn-1-yloxy)prop-1-en-1-yl)thiophene 11e. Yellow oil, yield: 36% (175 mg, 0.98 mmol). Eluent: gradient hexane/ethyl acetate. To a solution of propargyl alcohol (160 μL, 2.74 mmol) in THF (2.7 ml) was added dropwise Et_2Zn (1.4 ml, 1.4 mmol, 1 M in hexane). The resulting mixture was stirred until it turned cloudily white (30 min). and $Pd(PPh_3)_4$ (158 mg, 0.14 mmol) were then added to this suspension. The reaction was stirred until complete conversion (monitored by TLC). Then the mixture was concentrated and carefully purified by flash chromatography. **^{1}H NMR** (400 MHz, Acetone-d_6) δ 7.33 (d, *J* = 5.2 Hz, 1H), 7.08 – 7.07 (m, 1H), 7.02 –6.99 (m, 1H), 6.82 (d, *J* = 15.6 Hz, 1H), 6.12 (dtd, *J* = 15.8, 6.0, 1.7 Hz, 1H), 4.20 –4.17 (m, 4H, H1), 2.96 (dd, *J* = 4.3, 2.2 Hz, 1H). **^{13}C NMR** (101 MHz, Acetone-d_6) δ 142.6 (Cq), 128.3 (CH), 127.0 (CH), 126.4 (CH), 126.1 (CH), 125.5 (CH), 80.8 (Cq), 75.9 (CH), 70.2 (CH_2), 57.6 (CH_2). **(ESI) MS** calcd for $C_{10}H_{10}NaOS$ ($[M+Na]^+$) 201.03, found 201.12.

(*E*)-*N*-(3-(4-methoxyphenyl)allyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 11f. was obtained following the **GP-1** in 9 % overall yield (colourless oil, 260 mg, 0.73 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.26 (m, 5H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.51 (d, *J* =

15.8 Hz, 1H), 5.93 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.12 (d, *J* = 2.5 Hz, 2H), 3.96 (dd, *J* = 6.9, 1.3 Hz, 2H), 3.81 (s, 3H), 2.43 (s, 3H), 2.03 (t, *J* = 2.5 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.6 (Cq), 143.5 (Cq), 136.1 (Cq), 134.5 (CH), 129.5 (2CH), 128.9 (CH), 127.8 (2CH), 127.8 (2CH), 120.5 (CH), 114.0 (CH), 77.2 (Cq), 73.7 (CH), 55.3 (CH_2), 48.6 (CH_2), 35.7 (CH_3), 21.5 (CH_3).

(*E*)-4-methyl-*N*-(3-(naphthalen-2-yl)allyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide 11g was obtained following the **GP-1** in 5 % overall yield, (white solid, 160 mg, 0.43 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 – 7.79 (m, 5H), 7.71 (brs, 1H), 7.57 – 7.54 (m, 1H), 7.50 – 7.46, 2H), 7.35 – 7.33 (m, 2H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.22 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.19 (d, *J* = 2.5 Hz, 2H), 4.07 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.46 (s, 3H), 2.09 (t, *J* = 2.5 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.6 (Cq), 136.1 (Cq), 134.9 (Cq), 133.5 (Cq), 133.4 (Cq), 133.1 (CH), 129.5 (2CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.7 (2CH), 126.7 (CH), 126.4 (CH), 126.1 (CH), 123.4 (CH), 123.3 (CH), 76.6 (Cq), 73.8 (Cq), 48.6 (CH_2), 31.6 (CH_2), 21.5 (CH_3).

(*E*)-4-methyl-*N*-(prop-2-yn-1-yl)-*N*-(3-(3-(trifluoromethyl)phenyl)allyl)benzenesulfonamide 11h was obtained following the **GP-1** in 7 % overall yield, (white solid, 216 mg, 0.55 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.50 (m, 3H), 7.45 – 7.41 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.15 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.14 (d, *J* = 2.5 Hz, 2H), 4.02 (dd, *J* = 6.7, 1.4 Hz, 2H), 2.43 (s, 3H), 2.08 (t, *J* = 2.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.8 (Cq), 136.9 (Cq), 136.0 (Cq), 133.2 (CH), 131.0 (q, *J* = 32.2 Hz, Cq), 129.6 (CH), 129.6 (2CH), 129.1 (CH), 127.7 (2CH), 125.2 (CH), 124.5 (q, *J* = 3.7 Hz, CF_3), 124.0 (q, *J* = 272.5 Hz, CH), 123.2 (q, *J* = 3.8 Hz, CH), 76.5 (Cq), 74.0 (CH), 48.4 (CH_2), 36.2 (CH_2), 21.5 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.5.

***N*-cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl-3-*d*)benzenesulfonamide 11ba**. White solid, 50 % (150 mg). This reagent was prepared in accord with the procedure reported in literature. To the solution of *N*-cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (300 mg, 0.92 mmol) in THF dry (4 mL, 0.25 M) at -78 °C was dropwise added BuLi (1 mL, 1.6 M in Hexane). The mixture was kept under stirring for an hour. The mixture was then quenched with D_2O (1 mL). The resulting mixture was kept under stirring for an additional hour. The solvent was removed and the product was purified by flash chromatography. The NMR spectra correspond to the literature. [197] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.24 (m, 7H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.08 (dt, *J* = 14.9, 6.9 Hz, 1H), 4.13 (s, 2H), 3.99 (d, *J* = 6.9 Hz, 2H), 2.44 (s, 3H). **(ESI) MS** calcd for $C_{19}H_{18}DNNaO_2S$ ($[M+Na]^+$) 349.11, found 349.32

***N*-(cyclohex-2-en-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 13a**. White solid, 95 % (1.24 mg). To a solution of *N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide (1.13 g, 4.5 mmol, 1 equiv.) in CH_3CN was added K_2CO_3 (1.86 g, 13.5 mmol, 3 equiv.) and propargyl bromide (0.753 mL, 6.75 mmol, 1.5 equiv.) the mixture was heated to 70 °C and stirred overnight. Upon complete conversion, the mixture was diluted with AcOEt and H_2O then purified by flash chromatography. Spectra correspond to the literature.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 5.91 – 5.88 (m, 1H), 5.31 (d, *J* = 10.2 Hz, 1H), 4.52 – 4.47 (m, 1H), 4.13 (dd, *J* = 18.4, 2.4 Hz, 1H), 3.92 (dd, *J* = 18.5, 2.4 Hz, 1H), 2.43 (s, 3H), 2.18 (t, *J* = 2.4 Hz, 1H), 1.97 – 1.50 (m, 6H).

***N*-(but-2-yn-1-yl)-*N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide 13b**. White solid, 45 % (200 mg). To a solution of *N*-(cyclohex-2-en-1-yl)-4-

methylbenzenesulfonamide (368 mg, 1.46 mmol, 1 equiv.) in CH_3CN was added K_2CO_3 (604 g, 4.4 mmol, 3 equiv.) and propargyl bromide (0.25 mL, 80% in toluene, 2.19 mmol, 1.5 equiv.) the mixture was heated to 70 °C and stirred overnight. Upon complete conversion, the mixture was diluted with AcOEt and H_2O then purified by flash chromatography. Spectra correspond to the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 5.89 – 5.85 (m, 1H), 5.33 (d, *J* = 10.1 Hz, 1H), 4.53 – 4.49 (m, 1H9, 4.07 (dd, *J* = 18.2, 2.5 Hz, 0H), 3.88 (dd, *J* = 18.2, 2.4 Hz, 0H), 2.44 (s, 2H), 1.97 – 1.54 (m, 6H), 1.70 (t, *J* = 2.4 Hz, 2H).

dimethyl 2-(cyclohex-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate 13d. Colourless oil, 90 % (900 mg). To the solution of dimethyl malonate (1.38 mL, 12 mmol, 1.2 equiv.) in dry THF/DMF (12 mL, 4/1, 0.6 M) at 0 °C was dropwise added NaH (480 mg, 60 % in paraffin oil, 12 mmol., 1.2 equiv.). The mixture was kept under stirring for half an hour. Then, 2-bromo-cyclohexane was dropwise added (1.15 mL, 10 mmol, 1 equiv.). The reaction was stirred at room temperature overnight, quenched with ethanol, diluted with AcOEt, washed with water and dried. The crude was purified by flash chromatography yielding dimethyl 2-(cyclohex-2-en-1-yl)malonate (1.13 g, 53 %, 5.32 mmol). To the solution of dimethyl 2-(cyclohex-2-en-1-yl)malonate (850 mg, 4 mmol, 1 equiv.) in dry THF/DMF (6 mL, 4/1, 0.6 M) at 0 °C at 0 °C was dropwise added NaH (192 mg, 60 % in paraffin oil, 4.8 mmol, 1.2 equiv.). The mixture was kept under stirring for half an hour. Then, propargyl bromide was dropwise added (0.7 mL, 80 % in toluene, 6 mmol, 1.5 equiv.).The reaction was stirred at room temperature overnight, quenched with ethanol, diluted with AcOEt, washed with water and dried. The crude was then purified by flash chromatography. Spectra data correspond to the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.78 – 5.65 (m, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.13 – 3.08 (m, 1H), 2.87 (dd, *J* = 17.2, 2.7 Hz, 1H),

2.78 (dd, *J* = 17.2, 2.7 Hz, 1H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.95 – 1.26 (m, 6H).

(*E*)-(3-((4-(cyclohex-2-en-1-yloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)benzene 13e. Transparent oil, 50 % (209).To the solution of 4-(cinnamyloxy)but-2-yn-1-ol (300 mg, 1.5 mmol, 1 equiv.) in dry THF/DMF (2.5 mL, 4/1, 0.6 M) at 0 °C was dropwise added NaH (80 mg, 60 % in paraffin oil, 1.8 mmol., 1.2 equiv.). The mixture was kept under stirring for half an hour. Then, 2-bromo-cyclohexane was dropwise added (0.2 mL, 1.8 mmol, 1.2 equiv.). The reaction was stirred at room temperature overnight, quenched with ethanol, diluted with AcOEt, washed with water and dried. The crude was purified by flash chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 5H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.91 – 5.77 (m, 2H), 4.27 – 4.22 (m, 6H), 4.09 (brs, 1H), 2.08 – 1.94 (m, 2H), 1.87 – 1.68 (m, 3H), 1.61 – 1.54 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.5 (Cq), 133.2 (CH), 131.4 (CH), 128.5 (2CH), 127.7 (CH), 127.1 (CH), 126.5(2CH), 125.2 (CH), 83.1 (Cq), 81.7 (Cq), 71.7 (CH_2), 70.2 (CH_2), 57.4 (CH_2), 55.5 (CH_2), 28.0 (CH_2), 25.1 (CH_2), 19.0 (CH_2). **ESI-MS** calcd for $C_{19}H_{22}KO_2$ $[M+K]^+$ 321.13, found 321.27

allyldimethyl(prop-2-yn-1-yloxy)silane. Trasparent oil. Yield 48% (450 mg). Eluent: hexane/MTBE 9:1. Allylchlorodimethylsilane (1 mL, 6.6 mmol. 1.2 equiv.) was added dropwise to a solution of propargyl alcohol (350 µL, 6 mmol, 1 equiv.), trimethylamine (1.7 mL, 12 mmol, 2 equiv.) and DMAP (73 mg, 0.6 mmol, 0.1 equiv.) in dry DCM (12 mL, 0.5 M). The reaction mixture was stirred at room temperature for 16 h. Water was then added and the aqueous phase was extracted with DCM three times. Combined organic layers were then dried over Na_2SO_4 and filtered. The solvent was removed under reduce pressure and the crude product was purified by flash chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.7, 9.9, 8.1 Hz, 1H), 5.08 – 4.66 (m, 2H), 4.30 (d, *J* =

2.4 Hz, 2H), 2.41 (t, *J* = 2.4 Hz, 1H), 1.68 (dt, *J* = 8.1, 1.2 Hz, 2H), 0.18 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 133.6 (CH), 114.0 (CH_2), 82.0 (Cq), 73.2 (CH), 51.1 (CH_2), 24.3 (CH_2), -2.4 (CH_3).

1,4-bis(cinnamyloxy)but-2-yne 15a. Colorless oil. Yield 58% (4.3 g). Eluent: hexane/ethyl acetate 9:1; NaH (1.95 g, 49 mmol, 60% in mineral oil) was added to the solution of 1,4 - butyndiol (2.0 g, 23.23 mmol) in THF/DMF (3:1, M = 0.6) at 0 °C. The mixture was kept at 0 °C for 15 minutes. Cinnamyl chloride (6.8 mL, 48.8 mmol) was then added dropwise. The mixture was warmed up to r.t. and stirred for 24 hours. The reaction was quenched and then diluted with DCM (150 mL). The organic layer was washed with 2M HCl solution (100 mL), with H_2O (50 mL), dried over $MgSO_4$ and eventually concentrated under vacuum. The crude oil was purified by column chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 136.5 (Cq), 133.3 (CH), 128.6 (2CH), 127.8 (2CH), 126.5 (CH), 125.1 (CH), 82.5 (Cq), 70.3 (CH_2), 57.4 (CH_2). **(ESI) MS** calcd for $C_{22}H_{23}O_2$ ($[M+H]^+$) 319.17, found 319.25

1,4-bis(((*E*)-3-(thiophen-2-yl)allyl)oxy)but-2-yne 15b. This compound prepared following the **GP-1**. Yellow oil, yield: 50% (227 mg). Eluent: gradient hexane/ethyl acetate. **^{1}H NMR** (300 MHz, $CDCl_3$) 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). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.6 (Cq), 127.3 (CH), 126.4 (CH), 126.0 (CH), 124.7 (CH), 124.6 (CH), 82.5 (Cq), 69.9 (CH_2), 57.4 (CH_2). **(ESI) MS** calcd for $C_{18}H_{19}O_2S_2$ ($[M+H]^+$) 331.08, found 331.13

1,4-bis(((*E*)-3-(*o*-tolyl)allyl)oxy)but-2-yne 15c. Transparent oil, 34 %, 307 mg. This compound was obtained following the **GP-3** using using (E)-3-(o-tolyl)allyl acetate (1 g, 5.26 mmol, 2.1 eq.). **^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.6 (Cq), 135.5 (Cq), 131.1 (CH), 130.2 (CH), 127.6 (CH), 126.4 (CH), 126.1 (CH), 125.7 (CH), 82.4 (Cq), 70.5 (CH_2), 57.3 (CH_2), 19.8 (CH_3). **ESI-MS** calcd for $C_{24}H_{26}NaO_2$ $[M+Na]^+$ 369.18, found 369.40

1,4-bis(((*E*)-3-(3-fluoro-4-methylphenyl)allyl)oxy)but-2-yne 15d. White solid, 25 % (222 mg). This compound was obtained following the **GP-3** using (*E*)-3-(3-fluoro-4-methylphenyl)allyl acetate (1 g, 4.09 mmol, 2.1 eq.). **^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.38 (d, *J* = 244.3 Hz, Cq), 136.23 (d, *J* = 7.7 Hz, CH, Cq), 131.99 (d, *J* = 2.5 Hz, CH), 131.40 (d, *J* = 5.5 Hz, CH), 125.42 (CH), 124.29 (d, *J* = 17.6 Hz, Cq), 122.07 (d, *J* = 3.2 Hz, CH), 112.51 (d, *J* = 22.8 Hz, CH), 82.42 (Cq), 70.06 (CH_2), 57.45 (CH_2), 14.33 (d, *J* = 3.4 Hz, CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.7. **ESI-MS** calcd for $C_{24}H_{24}F_{26}NaO_2$ $[M+Na]^+$ 405.16, found 405.32

2-((*E*)-3-((4-(cinnamyloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)thiophene 15e. This compound prepared following the **GP-2**. Colourless oil. Yield: 40% (169 mg). Eluent: gradient hexane/ethyl acetate. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.22 (m, 5H), 7.19 – 7.15 (m, 1H), 7.00 – 6.92 (m, 2H), 6.77 (d, *J* = 15.7 Hz, 1H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.2 Hz, 1H), 6.12 (dt, *J* = 15.7, 6.2 Hz, 1H), 4.26 (s, 2H), 4.24 (dd, *J* = 6.2, 1.4 Hz, 2H), 4.20 (dd, *J* = 6.2, 1.4 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.6 (Cq), 136.5 (Cq), 133.3 (CH),

128.6 (CH), 127.8 (CH), 127.3 (CH), 126.5 (2CH), 126.4 (2CH), 126.0 (CH), 125.1 (CH), 124.7 (CH), 124.6 (CH), 82.5 (2Cq), 70.3 (CH_2), 69.9 (CH_2), 57.4 ($2CH_2$). **(ESI) MS** calcd for $C_{20}H_{21}O_2S$ ($[M+H]^+$) 325.13, found 325.22

1-((*E*)-3-((4-(cinnamyloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)-4-methoxybenzene 15f. This compound prepared following the **GP-2**. Yellow oil. Yield: 59% (225 mg). Eluent: gradient hexane/ethyl acetate. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 – 7.17 (m, 7H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 16.6 Hz, 1H), 6.59 (d, *J* = 17.1 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.1 Hz, 1H), 6.14 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.32 – 4.15 (m, 8H, H1), 3.80 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.3 (Cq), 136.5 (Cq), 133.2 (CH), 133.1 (CH), 129.2 (Cq), 128.5 (CH_2), 127.8 (2CH), 127.7 (2CH), 126.5 (CH), 125.1 (CH), 122.8 (CH), 113.9 (2CH), 82.5 (Cq), 82.3 (Cq), 70.4 (CH_2), 70.2 (CH_2), 57.4 (CH_2), 57.2 (CH_2), 55.2 (OCH_3). **(ESI) MS** calcd for $C_{23}H_{24}NaO_3$ ($[M+Na]^+$) 371.16, found 371.24

ethyl (*E*)-4-((4-(cinnamyloxy)but-2-yn-1-yl)oxy)but-2-enoate 15g. Colorless oil. Yield: 96% (745 mg). Eluent: gradient hexane/ethyl acetate; To a solution of 4-(cinnamyloxy)but-2-yn-1-ol (500 mg, 2.5 mmol) and PPh_3 (32 mg, 0.12 mmol) in benzene (12.4 mL) were sequentially added ethyl 2,3-butadienoate (590 μL, 5.08 mmol) and acetic acid (30 μL, 0.52 mmol). The reaction mixture was heated for 12 hours at 60 ºC and then cooled to r.t.. The crude has been concentrated and eventually purified by flash chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.16 (m, 5H), 6.95 (dt, *J* = 15.8, 4.5 Hz, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.2 Hz, 1H), 6.09 (dt, *J* = 15.8, 2.0 Hz, 1H), 4.26 – 4.17 (m, 10H), 1.29 (t, *J* = 7.1 Hz, 3H,). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1 (Cq), 143.3 (CH), 136.5 (Cq), 133.3 (CH), 128.6 (2CH), 127.8 (CH), 126.5 (CH), 125.0 (2CH), 121.8 (CH), 83.0 (Cq), 81.8 (Cq), 70.4 (CH_2), 68.2 (CH_2), 60.4 (CH_2), 58.2

(CH_2), 57.3 (CH_2), 14.2 (CH_3). **(ESI) MS** calcd for $C_{19}H_{22}NaO_4$ ($[M+Na]^+$) 337.14, found 337.28

ethyl (*E*)-4-((4-(((*E*)-3-(thiophen-2-yl)allyl)oxy)but-2-yn-1-yl)oxy)but-2-enoate 15h. Colorless oil. Yield: 53% (245 mg). Eluent: gradient hexane/ethyl acetate. To a solution of (*E*)-4-((3-(thiophen-2-yl)allyl)oxy)but-2-yn-1-ol (300 mg, 1.44 mmol) and PPh_3 (19 mg, 0.072 mmol) in benzene (7.2 mL) were sequentially added ethyl 2,3-butadienoate (343 µL, 2.95 mmol) and acetic acid (17 µL, 0.3 mmol). The reaction mixture was heated for 12 hours at 60 ºC (full conversion monitored by TLC), and then cooled to r.t.. The crude was concentrated and eventually purified by flash chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (m, 1H), 7.16 (m, 1H), 6.99 – 6.89 (m, 2H, H5), 6.76 (d, *J* = 15.7 Hz, 1H), 6.16 – 5.96 (m, 2H, H2), 4.29 – 4.13 (m, 10H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1 (Cq), 143.3 (Cq), 141.6 (CH), 128.3 (CH), 127.3 (CH), 126.4 (CH), 126.0 (CH), 124.6 (CH), 121.8 (CH), 82.9 (CH_2), 81.9 (CH_2), 70.0 (CH_2), 68.2 (CH_2), 60.4 (CH_2), 58.2 (Cq), 57.3 (Cq), 14.2 (CH_3). **(ESI) MS** calcd for $C_{17}H_{20}KO_4S$ ($[M+K]^+$) 359.07, found 359.24

((1*E*,1'*E*)-((4-methylpent-2-yne-1,4-diyl)bis(oxy))bis(prop-1-ene-3,1-diyl))dibenzene 15i. Colorless oil. Yield: 25 % (188 mg). Eluent: gradient hexane:ethylacetate; NaH (96 mg, 2.39 mmol, 60% in mineral oil) was added to a solution of 5-(cinnamyloxy)-2-methylpent-3-yn-2-ol (0.5 g, 2.17 mmol) in THF/DMF (3:1, M = 0.6) at 0°C. The mixture was kept at 0°C for 15 minutes and cinnamyl chloride (330 µL, 2.39 mmol) was added dropwise. The mixture was kept under stirring for 24 hours at r.t.. The reaction was quenched and diluted with DCM (15 mL). The organic layer was washed with a 2M HCl solution (10 mL), H_2O (5 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude oil was purified by column chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41

– 7.20 (m, 10H), 6.63 (m, 2H), 6.38 – 6.18 (m, 2H), 4.31 – 4.20 (m, 6H), 1.54 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.0 (Cq), 136.6 (Cq), 133.3 (CH), 131.7 (CH), 128.6 (2CH), 128.5 (2CH), 127.8 (CH), 127.5 (CH), 126.8 (CH), 126.5 (2CH), 126.5 (2CH), 125.3 (CH), 88.7 (Cq), 80.2 (Cq), 70.5 (CH_2), 70.2 (CH_2), 65.2 (Cq), 57.4 (CH_2), 28.9 ($2CH_3$). **(ESI) MS** calcd for $C_{24}H_{26}NaO_2$ ($[M+Na]^+$) 369.18, found 369.26

dimethyl 2-cinnamyl-2-(4-(cinnamyloxy)but-2-yn-1-yl)malonate 15j. Colourless oil. Yield: 58% (505 mg). Eluent: gradient hexane:ethylacetate. NaH (89 mg, 2.2 mmol, 60% in mineral oil) was added to a solution of dimethyl 2-cinnamylmalonate (0.5 mg, 2.0 mmol) in THF/DMF (3:1, M = 0.6) at 0°C. The mixture was kept at 0°C for 15 minutes and 4-(cinnamyloxy)but-2-yn-1-yl 4-methylbenzenesulfonate (790 mg, 2.2 mmol) was then added dropwise. The reaction was warmed up to r.t. and left under stirring overnight. The reaction was quenched with water and diluted with diethylether (100 mL). The organic phase was washed with a saturated solution of NaCl, dried over MgSO4 and concentrated under reduced pressure. The crude oil was purified by flash column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.15 (m, 5H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.2 Hz, 1H), 6.02 (dt, *J* = 15.5, 7.6 Hz, 1H), 4.22 (dd, *J* = 6.2, 1.4 Hz, 2H), 4.19 (t, *J* = 2.1 Hz, 2H), 3.76 (s, 6H), 2.97 (dd, *J* = 7.6, 1.3 Hz, 2H), 2.92 (t, *J* = 2.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.3 (2Cq), 136.9 (Cq), 136.6 (Cq), 134.6 (CH), 133.3 (CH), 128.6 (2CH), 128.5 (2CH), 127.8 (CH), 127.5 (CH), 126.5 (2CH), 126.3 (2CH), 125.2 (CH), 123.2 (CH), 81.3 (Cq), 79.4 (Cq), 69.9 (CH_2), 57.3 (Cq), 52.9 (OCH_3), 36.1 (CH_2), 23.4 (CH_2). **(ESI) MS** calcd for $C_{27}H_{28}KO_5$ ($[M+]^+$ K471.16, found 471.36.

***N*-cinnamyl-*N*-(4-(cinnamyloxy)but-2-yn-1-yl)-4-methylbenzenesulfonamide 15k.** Colorless oil. 60% (492 mg). Eluent: gradient hexane/ethyl acetate. DIAD (345 µL, 1.75 mmol) was added to a THF (17.5 mL) solution of 4-(cinnamyloxy)but-2-yn-1-ol (352 mg, 1.74 mmol), *N*-cinnamyl-4-methylbenzenesulfonamide (500 mg, 1.74 mmol) and PPh_3 (456 mg, 1.74 mmol) in under an argon atmosphere. The mixture was stirred at room temperature overnight. The mixture was then concentrated and the crude residue was purified by flash chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.15 (m, 12H, ArH), 6.58 (d, *J* = 15.8 Hz, 2H, H1), 6.15 (m, 2H), 4.19 (m, 2H), 4.05 (d, *J* = 6.09 Hz, 2H), 4.00 (d, *J* = 6.92 Hz, 2H), 3.98 – 3.96 (m, 2H), 2.39 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.5 (Cq), 136.3 (Cq), 136.0 (Cq), 136.0 (Cq), 134.7 (CH), 133.1 (CH), 129.4 (2CH), 128.5 (2x2CH), 128.0 (Cq), 127.8 (Cq), 127.7 (2CH), 126.5 (2CH), 126.4 (2CH), 124.9 (CH), 122.9 (CH), 81.6 (Cq), 79.2 (Cq), 70.0 (CH_2), 56.9 (CH_2), 48.7 (CH_2), 36.2 (CH_2), 21.4 (CH_3). **(ESI) MS** calcd for $C_{29}H_{29}NNaO_3S$ ($[M+Na]^+$) 494.18, found 494.30.

4,4,11,11-tetramethyl-5,10-dioxa-4,11-disilatetradeca-1,13-dien-7-yne.
Trasparent oil. Yield 30% (250 mg). Eluent: gradient hexane/ethyl acetate. Allylchlorodimethylsilane (1 mL, 6.6 mmol, 2.2 equiv.) was added dropwise to the solution of 2-butyne-1,4-diol (260 mg, 3 mmol, 1 equiv.), trimethylamine (1.7 mL, 12 mmol, 4 equiv.) and DMAP (73 mg, 0.6 mmol, 0.2 equiv.) in dry DCM (9 mL, 0.33 M). The reaction mixture was stirred at room temperature for 16 h. Water was then added and the aqueous phase was extracted with DCM three times. Combined organic layers were then dried over Na_2SO_4 and filtered. The solvent was removed under reduce pressure and the crude product has been purified by flash chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.91 – 5.53 (m, 2H), 4.95 – 4.86 (m, 4H), 4.33 (s, 4H), 1.69 -1.65 (m, 4H), 0.17 (s, 12H). **^{13}C**

NMR (300MHz, $CDCl_3$) δ 133.6 (CH), 114.0 (CH_2), 83.2 (Cq), 51.4 (CH_2), 24.3 (CH_2), 2.4 ($2CH_3$). **(ESI) MS** calcd for $C_{14}H_{26}O_2Si_2Na$ ($[M+Na]^+$) 305.61, found 305.67

Complex A. This cluster was obtained following the **GP-4** using dimethyldisulfide. Deep red crystals. 60% (58 mg, 0.039 mmol). **^{31}P NMR** (162 MHz, $CDCl_3$): δ 17.42. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.31 (m, 45H), 1.00 (s, 9H).

Complex B. This cluster was obtained following the **GP-4** using diphenyldisulfine. Deep red powder. 80% (90 mg, 0.05 mmol). **^{31}P NMR** (162 MHz, $CDCl_3$): δ 16.28. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.27 (m, 9H), 7.15 - 7.09 (m, 36H), 6.92 (t, *J* = 7.6 Hz, 3H), 6.64 (t, *J* = 7.8 Hz, 6H), 6.23 (d, *J* = 7.35 Hz, 6H).

4'-methylene-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] 12a was isolated following general procedure **GP-5** using *N*-allyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide as substrate (75 mg, 0.3 mmol, 1 equiv.). Colourless oil. 45% (33.6 mg, 0.067 mmol). Eluent: ethyl acetate/hexane 1:9. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 17.6, 8.3 Hz, 4H), 7.33 (dd, *J* = 7.68, 5.33 Hz, 4H), 4.87 (t, *J* = 1.95 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). **^{13}C NMR** (75 MHz, $CDCl_3$): 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 (CH_2), 57.6 (CH_2), 56.7 (CH_2), 52.0 ($2CH_2$), 44.5 (Cq), 32.9 (CH_2), 30.3 (CH_2), 21.52 ($2CH_3$), 20.82 (CH_2). **HRMS** calcd for $C_{38}H_{38}N_2NaO_4S_2$ ($[M+Na]^+$) 673.2165, found 673.2163

(4*S*,5*R*)-4'-((*Z*)-benzylidene)-4-phenyl-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3' pyrrolidine] 12b and **(4*S*,5*S*)-4'-((*Z*)-benzylidene)-4-phenyl-1',2-ditosyl-1,2,3,4,6,7 hexahydrospiro[isoindole-5,3'-pyrrolidine] 12b**' were isolated following general procedure **GP-4** using **11b** (97.5 mg, 0.3 mmol, 1 equiv.) White solid. Yield 61% (33.6 mg, **^{1}H NMR** *dr* 39:62). Gradient: hexane/ethyl acetate. **^{1}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}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 ($2CH_2$), 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). **HRMS** calcd for $C_{38}H_{38}N_2NaO_4S_2$ ($[M+Na]^+$) 673.2165, found 673.2163

(4*S*,5*R*)-4'-((*Z*)-benzylidene)-1',2-bis(methylsulfonyl)-4-phenyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] 12c and **(4*S*,5*S*)-4'-((*Z*)-benzylidene)-1',2-bis(methylsulfonyl)-4-phenyl-1,2,3,4,6,7-**

hexahydrospiro[isoindole-5,3'-pyrrolidine] 12c' were isolated following **GP-4** using **11c** (50 mg, 0.2 mmol.).

12c: Colourless oil, 20 % (10.1 mg, 0.02 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) 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). **^{13}C NMR** (75 MHz, $CDCl_3$) 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 (CH_2), 57.0 (CH_2), 56.4 (CH_2), 51.3 (CH_2), 50.6 (Cq), 47.2 (CH), 35.0 (CH_3), 34.9 (CH_3), 26.1 (CH_2), 21.3 (CH_2). **ESI-MS** calcd for $C_{26}H_{30}KN_2O_4S_2$ $[M+Na]^+$ 537.13 found 537.35; **12c'**: Colourless oil, 48 % (23.7 mg, 0.048 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2 (Cq), 138.2 (Cq), 136.0 (Cq), 132.7 (Cq), 131.1 (Cq), 128.8 (2x2CH), 128.7 (2CH), 128.4 (2CH), 127.9 (CH), 127.6 (CH), 122.5 (CH), 57.1 (CH_2), 55.9 (CH_2), 50.7 (CH_2), 49.6 (CH_2), 47.9 (Cq), 35.5 (CH_3), 34.8 (CH_3), 28.3 (CH_2), 20.7 (CH_2). **ESI-MS** calcd for $C_{26}H_{30}KN_2O_4S_2$ $[M+Na]^+$ 537.13 found 537.33

(3*R*,4'*S*)-4-((*Z*)-benzylidene)-4'-phenyl-1',4,4',5,6',7'-hexahydro-2*H*,3'*H*-spiro[furan-3,5'-isobenzofuran] 12d and **(3*S*,4'*S*)-4-((*Z*)-benzylidene)-4'-phenyl-1',4,4',5,6',7'-hexahydro-2*H*,3'*H*-spiro[furan-3,5'-isobenzofuran] 12d**' were isolated following **GP-1** using **11d** as reagent (58 mg, 0.34 mmol). Yellow pale oils. Yield 57%. **12d** (6.6 mg, 0.02 mmol) and **12d'** (26.5 mg, 0.077 mmol). The two diastereomers of **12d** were separated by chromatography.

Eluente: hexane:ethyl acetate gradient. **12d:** **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 – 7.08 (m, 6H), 7.03 – 7.00 (m 2H), 6.82 – 6.73 (m, 2H), 4.97 (t, *J* = 2.7 Hz, 1H), 4.86 (dd, *J* = 14.3, 2.6 Hz, 1H), 4.72 (brs, 2H), 4.64 (dd, *J* = 14.3, 2.6 Hz, 1H), 4.49 – 4.38 (m, 2H), 4.09 (d, *J* = 8.4 Hz, 1H), 3.63 (d, *J* = 8.4 Hz, 1H), 3.48 (brs, 1H), 2.40 - 2.28 (m, 1H), 2.23 – 2.03 (m, 2H), 1.67 – 1.49 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.1 (Cq), 139.4 (Cq), 137.0 (C6a), 132.3 (Cq), 132.2 (Cq), 129.6 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 126.8 (CH), 126.5 (CH), 122.8 (CH), 78.3 (CH_2), 77.4 (CH_2) 77.2 (CH_2), 71.4 (CH_2), 51.3 (Cq), 46.2 (CH), 26.2 (CH_2), 20.3 (CH_2). **(ESI) MS** calcd $C_{24}H_{24}NaO_2$ ($[M+Na]^+$) 367.1672, found 367.1674. **12d':** **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 6.97 (m, 10H), 6.34 (s, 1H), 4.77 (dd, *J* = 14.3, 2.6 Hz, 1H), 4.74 – 4.61 (m, 2H), 4.48 (dd, *J* = 14.2, 2.5 Hz, 1H), 4.52 - 4.41 (m, 2H), 3.68 (d, *J* = 8.9 Hz, 1H), 3.49 (brs, 1H), 3.12 (d, *J* = 8.8 Hz, 1H), 2.19 (q, *J* = 19.1, 18.5 Hz, 2H), 1.94 (t, *J* = 4.2 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.2 (Cq), 139.3 (Cq), 137.1 (Cq), 133.8 (Cq), 132.1 (Cq), 128.5 (CH), 128.2 (CH), 127.2 (CH), 126.8 (CH), 119.8 (CH), 77.5 (CH_2), 76.4 (CH_2), 76.3 (CH_2), 70.9 (CH_2), 49.9 (Cq), 46.4 (CH), 28.3 (CH_2), 19.4 (CH_2). **HRMS** calcd $C_{24}H_{24}NaO_2$ ($[M+Na]^+$) 367.1672, found 367.1671

(3*R*,4'*S*,*Z*)-4'-(thiophen-2-yl)-4-(thiophen-2-ylmethylene)-1',4,4',5,6',7'-hexahydro-2*H*,3'*H*-spiro[furan-3,5'-isobenzofuran] 12e and **(3*R*,4'*S*,*Z*)-4'-(thiophen-2-yl)-4-(thiophen-2-ylmethylene)-1',4,4',5,6',7'-hexahydro-2*H*,3'*H*-spiro[furan-3,5'-isobenzofuran] 12e'** were isolated following **GP-1** using **11e** as reagent (61 mg, 0.24 mmol). Yallow pale oils. Yields 67%. **12e** (14 mg, 0.04 mmol), **12e'** (27 mg, 0.075 mmol). The two diastereomers of **12e** were separated by chromatography. Eluente: hexane:ethyl acetate gradient. **12e**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 5.4 Hz, 1H), 7.10 (dd, *J* = 5.0, 1.0 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.85 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.63 (dd, *J* = 9.3, 3.2 Hz, 2H), 5.52 (t, *J* = 2.7 Hz, 1H), 4.79 (dd, *J* = 14.7, 2.6 Hz, 1H), 4.68 –

4.65 (m, 2H), 4.63 (dd, *J* = 14.8, 2.9 Hz, 1H), 4.52 - 4.48 (m, H2), 4.06 (d, *J* = 8.5 Hz, 1H), 3.75 (brs, 1H), 3.65 (d, *J* = 8.5 Hz, 1H), 2.43 – 2.19 (m, 2H), 2.15 – 1.97 (m, 1H), 1.71 – 1.48 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.2 (Cq), 142.4 (Cq), 140.8 (Cq), 132.6 (Cq), 131.9 (Cq), 127.3 (CH), 126.6 (CH), 126.4 (CH), 126.9 (CH), 125.2 (CH), 124.1 (CH), 115.2 (CH_2), 77.8 (CH_2), 77.3 (CH_2), 76.9 (CH_2), 71.5 (CH_2), 51.4 (Cq), 41.1 (CH), 26.1 (CH_2), 20.2 (CH_2). **(ESI) MS** calcd $C_{20}H_{20}NaO_2S_2$ ($[M+Na]^+$) 379.4874 ,found 379.4872. **12e'**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 5.1 Hz, 1H), 7.19 (d, *J* = 5.2 Hz, 1H), 7.05 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.88 (d, *J* = 3.7 Hz, 1H), 6.82 (dd, *J* = 3.5, 1.1 Hz, 1H), 6.49 (t, *J* = 2.6 Hz, 1H), 4.74 (dd, *J* = 14.8, 2.6 Hz, 1H), 4.68 (brs, 2H), 4.60 (dd, *J* = 14.8, 2.6 Hz, 1H), 4.54 (brs, 2H), 3.75 (s, 1H), 3.74 (d, *J* = 8.9 Hz, 1H) 3.32 (d, *J* = 8.9 Hz, 1H), 2.26 – 1.85 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0 (CH), 142.8 (Cq), 140.9 (Cq), 133.7 (Cq), 132.4 (Cq), 127.4 (CH), 126.5 (CH), 126.5 (CH), 126.0 (CH), 125.6 (CH), 124.7 (CH), 112.6 (CH_2), 77.5 (CH_2), 77.4 (CH_2), 76.4 (CH_2), 71.6 (CH_2), 49.6 (Cq), 41.4 (CH_2), 27.7 (CH_2), 19.2 (CH_2). **HRMS** calcd $C_{20}H_{20}NaO_2S_2$ ([M+Na]+) 379.4874 , found 379.4875

(4*S*,5*S*)-4'-((*Z*)-4-methoxybenzylidene)-4-(4-methoxyphenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] 12f (major) and **(4*S*,5*R*)-4'-((*Z*)-4-methoxybenzylidene)-4-(4-methoxyphenyl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] 12f'** (minor) were isolated following **GP-3** using **11f** (71.09 mg, 0.2 mmol) as reagent. Yield 62 % (colourless oil, 43.2 mg, 0.062 mmol, **^{1}H NMR** *dr* 65:35). **^{1}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}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 (2C), 129.9, 129.8, 129.7, 129.6, 129.2 (2C), 128.9, 127.7 (2C), 127.6, 127.5, 127.4, 124.3, 121.3, 114.0, 113.9, 113.7 (2C), 113.3 (2C), 60.4, 57.5, 57.3, 57.0, 56.4, 56.1, 55.4, 55.3, 55.2 (2C), 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-MS** calcd for $C_{40}H_{42}KN_2O_6S_2$ $[M+K]^+$ 749.21 found 749.47

(4*S*,5*S*,*Z*)-4'-(naphthalen-1-ylmethylene)-4-(naphthalen-2-yl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] 12g (major) and **(4*S*,5*R*,*Z*)-4'-(naphthalen-1-ylmethylene)-4-(naphthalen-2-yl)-1',2-ditosyl-1,2,3,4,6,7-hexahydrospiro[isoindole-5,3'-pyrrolidine] 12g'** (minor) were isolated following **GP-3** using **11g** (75 mg, 0.2 mmol) as reagent. Yield 69 % (52 mg, 0.07 mmol, **^{1}H NMR** *dr* 80:20). **^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) 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 (2xCH), 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-MS** calcd for $C_{46}H_{43}N_2O_4S_2$ $[M+H]^+$ 751.27 found 751.47

(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] 12h (major) 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] 12h** (minor) were isolated following **GP-3** using **11h** (78.6 mg, 0.2 mmol) as reagent 65 % (colourless oil, 51.4 mg, 0.065 mmol, ^{1}H NMR *dr* 56:44). **^{1}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}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}F NMR** (376 MHz, $CDCl_3$) δ -62.6, -62.6, -62.7, -63.0. **ESI-MS** calcd for $C_{40}H_{37}F_6N_2O_4S_2$ $[M+H]^+$ 787.21 found 787.44

3-methylene-1-tosyl-2,3,3a,6,7,7a-hexahydro-1*H*-indole 14a was isolated 69 % (colourless oil, 60.1 mg, 0.21 mmol) following **GP-3** using **13a** (87 mg, 0.3

mmol). Spectroscopic data correspond to the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) d 7.73 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.80 – 5.77 (m, 1H), 5.65 – 5.60 (m, 1H), 4.98 (d, *J* = 2.2 Hz, 1H), 4.84 (d, *J* = 2.3 Hz, 1H), 4.01 – 3.84 (m, 3H), 2.73 (brs, 1H), 2.42 (s, 3H), 2.11 – 1.89 (m, 3H), 1.63 – 1.51 (m, 1H).

3-ethylidene-1-tosyl-2,3,3a,6,7,7a-hexahydro-1*H*-indole 14b was isolated 66 % (colourless oil, 60 mg, 0.2 mmol) using **13b** as reagent (91 mg, 0.3 mmol). **^{1}H NMR** (400 MHz, CDCl3) d 7.73 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.77 -5.75 (m, 1H), 5.62 – 5.57 (m, 1H), 5.24 – 5.17 (m, 1H), 4.07 – 4.01 (m, 1H), 3.86 – 3.79 (m, 4H), 2.71 (brs, 1H), 2.42 (s, 3H), 2.20 – 1.86 (m, 4H), 1.64 – 1.55 (m, 4H). **^{13}C NMR** (101 MHz, CDCl3) d 143.3 (Cq), 138.5 (2Cq), 129.7 (2CH), 128.1 (CH), 127.3 (2CH), 124.6 (CH), 117.8 (CH), 58.8 (CH), 48.6 (CH_2), 42.6 (CH), 26.1 (CH_2), 23.3 (CH_2), 21.5 (CH_3), 14.5 (CH_3). **ESI-MS** calcd for $C_{17}H_{22}NO_2S$ $[M+H]^+$ 304.14 , found 304.06

2,2-dimethyl-3-methylene-1-tosyl-2,3,3a,6,7,7a-hexahydro-1*H*-indole 14c was isolated 32% (colourless oil, 20.3 mg, 0.06 mmol) following the **GP-3** using **13c** as reagent (63.5 mg, 0.2 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) d 7.78 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 4.9 Hz, 2H), 5.90 – 5.50 (m, 2H), 4.98 (d, *J* = 2.9 Hz, 1H), 4.78 (d, *J* = 2.4 Hz, 1H), 3.88 (dt, *J* = 9.0, 6.6 Hz, 1H), 2.81 (brs, 1H), 2.41 (s, 3H), 2.17 – 1.86 (m, 2H), 1.73 (s, 3H), 1.48 (s, 3H), 1.33- 1.25 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) d 157.0 (Cq), 142.6 (Cq), 129.4 (2CH), 129.4 (Cq), 127.0 (2CH), 123.9 (CH), 123.8 (CH), 103.4 (CH2), 67.1 (Cq), 56.4 (CH), 37.8 (CH), 30.0 (CH_2), 29.9 (CH_3), 29.2 (CH_3), 23.5 (CH_2), 21.5 (CH_3). **ESI-MS** calcd for $C_{18}H_{24}NO_2S$ $[M+H]^+$ 318.15 , found 318.23

dimethyl 3-methylene-2,3,3a,6,7,7a-hexahydro-1*H*-indene-1,1-dicarboxylate **14d** was isolated 70 % (colourless oil, 52.3 mg, 0.21 mmol) following **GP-3** using **13d** as reagent (75 mg, 0.3 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.88 – 5.83 (m, 1H), 5.77 – 5.72 (m, 1H), 4.97 (d, *J* = 2.2 Hz, 1H), 4.83 (q, *J* = 2.6 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.32 (dq, *J* = 17.8, 2.5 Hz, 1H), 3.21 (brs, 1H), 2.89 – 2.81 (m, 2H), 2.04 – 1.99 (m, 2H), 1.35 – 1.07 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.2 (Cq), 170.2 (Cq), 151.1 (Cq), 126.4 (2CH), 107.6 (CH_2), 62.4 (Cq), 52.7 (CH_3), 52.5 (CH_3), 43.0 (CH_2), 42.8 (CH_2), 37.7 (CH_2), 24.4 (CH_2), 21.3 (CH_2). **ESI-MS** calcd for $C_{14}H_{19}O_4$ $[M+H]^+$ 251.13, found 251.19

3a*S*,4*R*,5*R*,8b*R*)-4,5-diphenyl-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran 16a was synthesized following **GP-6** using **15a** (190 mg, 0.6 mmol) as reagent at 45°C for 48 hours. Pale yellow solid. Yield 87 % (166.7 mg, *dr* 93:7 ratio from **^{1}H NMR**). Eluent: gradient hexane/ethyl acetate. **^{1}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, 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}C NMR** (101 MHz, CD_2Cl_2) δ 141.12 (Cq), 138.61 (Cq), 135.54 (Cq), 133.04 (Cq), 130.07 (Cq), 128.77 (CH), 128.01 (CH), 127.88 (CH), 126.88 (CH), 126.61 (CH), 76.45 (CH_2), 75.87 (CH_2), 70.12 (CH_2), 70.00 (CH_2), 49.00 (CH), 47.70 (CH), 44.13 (CH), 43.07 (CH). **HRMS** calcd for $C_{22}H_{22}KO_2$ ($[M+K]^+$) 357.1252, found 357.1253

(3a*R*,4*S*,5*S*,8b*R*)-4,5-di(thiophen-2-yl)-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran 16b was synthesized using **GP-2** using **15b** (112 mg, 0.34 mmol) as reagent at 45°C for 24 hours. White solid. Yield 65% (72 mg, *dr* 96:4 ratio from **^{1}H NMR**). The product was crystallized from hexane:ethylacetate and used for XRD. Eluent: hexane/ethyl acetate 8:2 **^{1}H**

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, 2.55 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 143.17 (C2'), 141.49 (C2''), 135.31 (C6a), 131.89 (C8a), 126.60 (C3''), 126.47, 126.32 (C4'', C4'), 124.94 (C5''), 124.78 (C3'), 123.81 (C5'), 76.29 (C8), 75.49 (C6), 70.20 (C3), 69.67 (C1), 44.11 (C3a), 43.77 (C4), 43.52 (C8b), 43.34 (C5). **HRMS** calcd for $C_{18}H_{18}KO_2S_2$ ($[M+K]^+$) 369.0383, found 369.0382

(3a*R*,4*S*,5*S*,8b*S*)-4,5-di-*o*-tolyl-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 16c was isolated following **GP-4** using **15c** (colourless oil, 70 mg, 0.2 mmol) as reagent 63 % (43.4 mg, 0.12 mmol, *dr* 98:2) **^{1}H 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 (CH_2), 75.5 (CH_2), 70.1 (CH_2), 69.8 (CH_2), 43.9 (CH), 43.4 (CH), 43.3 (CH), 39.6 (CH), 19.8 (CH_3), 18.5 (CH_3). **ESI-MS** calcd for $C_{24}H_{26}NaO_2$ $[M+Na]^+$ 369.18 , found 369.20

(3a*R*,4*S*,5*S*,8b*S*)-4,5-bis(3-fluoro-4-methylphenyl)-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 16d was isolated following **GP-4** using

15d (colourless oil, 38.2 mg, 0.1 mmol) as reagent 65 % (24.8 mg, 0.065 mmol, ^{1}H NMR *dr* 98:2). **^{1}H 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* = 7.1 Hz, Cq), 137.4 (d, *J* = 6.8 Hz, Cq), 134.9 (Cq), 132.7 (Cq), 130.8 (d, *J* = 5.4 Hz, CH), 130.6 (d, *J* = 5.4 Hz, CH), 130.1 (Cq), 124.4 (Cq), 123.5 (d, *J* = 2.7 Hz, CH), 123.2 (d, *J* = 17.3 Hz, CH), 122.9 (d, *J* = 17.1 Hz, CH), 115.9 (d, *J* = 22.3 Hz, Cq), 114.7 (d, *J* = 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* = 3.5 Hz, $2CH_3$). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -118.2. **ESI-MS** calcd for $C_{24}H_{24}F_2NaO_2$ $[M+Na]^+$ 405.16 , found 405.10

(3a*S*,4*S*,5*S*,8b*R*)-4-phenyl-5-(thiophen-2-yl)-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 16e and **(3a*R*,4*R*,5*R*,8b*R*)-5-phenyl-4-(thiophen-2-yl)-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 16e'** were obtained following **GP-2** using **15e** as reagent (194 mg, 0.6 mmol) at 45°C for 24 hours. Pale yellow solid. Yield 58 % (112.7 mg, dr 92:8 by **^{1}H NMR**) Regioisomeric ratio 60:40 for **6c**. Eluent: gradient hexane/ethyl acetate 1**6e** and **16e'** were isolated in mixture. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.14 – 7.11 (m, 3H), 7.04 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.98 (dd, J = 5.1, 1.2 Hz, 1H), 6.81 – 6.78 (m, 4H), 6.74 – 6.70 (m, 2H), 6.29 (d, *J* = 3.43 Hz, 1H), 6.26 (d, *J* = 2.85 Hz, 1H), 4.77 – 4.66 (m, 4H), 4.54 – 4.37 (m, 4H), 4.22 – 4.16 (m, 2H), 4.01 (bd, *J* = 4.0 Hz, 1H), 3.97 – 3.88 (m, 2H), 3.80 (d, *J* = 6.6 Hz, 1H), 3.72 – 3.62 (m, 3H), 3.43 – 3.32 (m, 4H), 2.91 – 2.77 (qd, *J* = 11.1, 6.8 Hz, 1H), 2.73 – 2.57 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.2, 141.5, 140.2, 137.9, 135.4, 135.0, 132.2, 132.0, 129.3, 127.9 (2C), 127.8, 126.9, 126.6, 126.5, 126.3, 126.2, 124.8, 124.5, 123.4, 76.2, 76.2, 75.5, 75.5, 70.2, 69.9, 69.8, 69.5, 48.5, 47.6, 43.9, 43.6, 43.6,

43.5, 42.9, 42.9. **HRMS** calcd for $C_{20}H_{20}NaO_2S$ ([M+Na]$^+$) 347.1089 , found 347.1088

(3a*S*,4*R*,5*R*,8b*R*)-5-(4-methoxyphenyl)-4-phenyl-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran 16f and **(3a*S*,4*R*,5*R*,8b*R*)-4-(4-methoxyphenyl)-5-phenyl-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran 16f'** were synthesized following **GP-2** using **15f** (60 mg, 0.17 mmol) as reagent at 45°C for 48 hours. Pale yellow oil. Yield 51% (30.1 mg, *dr* 97:3 **^{1}H NMR**). Regioisomeric ratio 50:50. Eluent: gradient hexane/ethyl acetate 1**6f** and **16f'** were isolated in mixture. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.15 – 7.03 (m, 6H), 6.67 – 6.52 (m, 12H), 4.77 – 4.68 (m, 4H), 4.49 – 4.38 (m, 4H), 4.19 (t, J = 6.9 Hz, 2H), 3.72 (s, 6H), 3.86 - 3.62 (m, 6H), 3.37 – 3.26 (m, 4H), 2.80 – 2.57 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4, 158.1, 140.5, 137.9, 135.6, 135.3, 132.4, 132.4, 132.1, 130.5 (2C), 129.8, 129.7 (2C), 129.2, 128.3, 127.7, 127.6, 126.6, 126.3, 113.1, 113.0, 76.2, 75.6, 69.9 (2C), 55.2, 55.0, 48.7, 47.8, 47.4, 47.2, 46.5, 46.4, 43.7, 43.7, 42.9, 42.6. **HRMS** calcd for $C_{23}H_{24}KO_3$ ([M+K]$^+$) 387.1366 , found 387.1365

ethyl (3a*R*,4*R*,5*R*,8b*R*)-5-phenyl-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran-4-carboxylate 16g and ethyl **(4*S*,5*S*,5a*S*,8a*R*)-5-phenyl-1,3,4,5,5a,6,8,8a-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran-4-carboxylate 16g'** were isolated following **GP-2** using **15g** (114.6 mg, 0.36 mmol) as reagent at 45 °C for 24 hours. White solid. Yield 67 % (75.3 mg, *dr* 98:2 ratio from **^{1}H NMR**). Regioisomeric ratio 50:50. Eluent: gradient hexane/ethyl acetate **6e** and **6'e** were isolated in mixture. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.12 (m, 10H), 4.66 – 4.65 (m, 4H), 4.49 – 4.26 (m 4H), 4.17 – 4.02 (m, 5H), 3.79 – 3.71 (m, 3H), 3.68 – 3.40 (m, 5H), 3.33 – 3.22 (m, 2H), 3.18 – 3.01 (m, 2H), 2.59 – 2.48 (m, 3H), 0.98 (t, J = 7.17 Hz, 3H, CH_3), 0.82 (t, J =7.15 Hz, 3H, CH_3). **^{13}C NMR** (75 MHz,

$CDCl_3$) δ 171.5, 170.7, 139.5, 137.7, 134.0, 132.3, 130.8, 129.0, 128.3, 128.3, 128.0, 127.6, 127.1, 75.8, 75.6, 75.4, 75.4, 70.0, 70.0, 69.1, 68.9, 60.5, 60.3, 48.9, 47.9, 45.8, 43.0, 42.9, 42.8, 42.0, 40.9, 13.8, 13.6. **HRMS** calcd for $C_{19}H_{23}0_4$ ($[M+H]^+$) 315.3892, found 315.3893

ethyl (3a*R*,4*S*,5*S*,8b*R*)-5-(thiophen-2-yl)-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran-4-carboxylate 16h and **methyl (4*S*,5*S*,5a*R*,8a*R*)-5-(thiophen-2-yl)-1,3,4,5,5a,6,8,8a-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran-4-carboxylate 16h'** were isolated following **GP-2** using **15f** (52 mg, 0.16 mmol) as reagent at 45 °C for 24 hours. Regioisomeric ratio 75:25 for **16h**; Diasteromeric ratio 97:3 (ratio from ^{1}H NMR). White solid. Yield 70 % (36.4 mg, 0.11 mmol). Eluent: gradient hexane/ethyl acetate **16h** and **16h'** were isolated in mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.17 (m, 1H), 6.94 – 6.82 (m, 2H), 4.69 – 4.60 (m, 2H), 4.52 – 4.46 (m, 2H), 4.37 (bd, *J* = 5.7 Hz, 1H), 4.27 (t, *J* = 7.3 Hz, 1H), 4.14 – 4.09 (m, 1H), 3.99 – 3.80 (m, 2H), 3.62 (dd, *J* = 11.5, 7.1 Hz), 3.57 – 3.48 (m, 2H), 3.42 (dd, *J* = 11.3, 7.8 Hz), 3.18 – 3.08 (m, 1H), 3.02 (dd, *J* = 11.7, 6.4 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.53 – 2.48 (m, 1H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.3, 170.7, 142.2, 140.9, 134.3, 133.9, 132.1, 130.6, 126.8, 126.7, 126.6, 125.3, 125.2, 124.0, 77.2, 75.9, 75.7, 75.4, 70.3, 70.0, 69.3, 68.8, 60.9, 60.7, 49.2, 48.5, 44.0, 43.2, 42.2, 41.2, 41.0, 38.4, 13.9, 13.8. **HRMS** calcd for $C_{17}H_{20}NaO_4S$ ($[M+Na]^+$) 343.3923 , found 343.3923

(3a*S*,4*R*,5*R*,8b*R*)-1,1-dimethyl-4,5-diphenyl-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 16i and **(3a*S*,4*R*,5*R*,8b*R*)-8,8-dimethyl-4,5-diphenyl-1,3,3a,4,5,6,8,8b-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 16i'** were isolated following **GP-2** using **15i** (120 mg, 0.35 mmol) as reagent at 70°C for 48 hours. Regioisomeric ratio 60:40 for **16i**; Diasteromeric ratio 94:6 (ratio

from **^{1}H NMR**). White solid. Yield 88 % (107.3 mg, 0.31 mmol). Eluent: gradient hexane/ethyl acetate **16i** and **16i'** were isolated in mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 – 7.03 (m, 6H), 6.67 – 6.64 (m, 4H), 4.92 – 4.75 (m, 2H), 4.45 – 4.40 (m, 2H), 4.39 – 4.35 (m, 1H), 4.25 (t, *J* = 6.7 Hz, 1H), 3.84 – 3.79 (m, 2H), 3.76 – 3.72 (m, 3H), 3.37 – 3.33 (m, 3H), 3.28 (dd, *J* = 10.6, 7.7 Hz, 1H), 2.97 (qd, *J* = 11.3, 6.7 Hz, 1H), 2.76 – 2.62 (m, 2H), 2.51 (bd, *J* = 9.2 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3, 140.2, 139.7, 137.7, 137.7, 136.4, 134.0, 131.9, 129.5, 128.3, 128.2, 127.6, 127.5, 126.6, 126.6, 126.3, 126.3, 87.7, 80.5, 76.1, 74.5, 73.8, 69.6, 69.3, 53.6, 48.9, 48.5, 47.2, 47.2, 43.3, 42.5, 40.3, 29.1, 27.9, 26.5, 24.9. **HRMS** calcd for $C_{24}H_{26}KO_2$ ($[M+K]^+$) 385.1573, found 385.1572

Dimethyl (3a*S*,4*R*,5*R*,8b*R*)-4,5-diphenyl-1,3,3a,4,5,6,8,8b-octahydro-7*H*-indeno[4,5-*c*]furan-7,7- dicarboxylate 16j and **dimethyl (4*R*,5*S*,5a*R*,8a*R*)-4,5-diphenyl-1,3,4,5,5a,6,8,8a-octahydro-7*H*-indeno[4,5-*c*]furan-7,7-dicarboxylate 16j'** were isolated following **GP-2** using **15j** (158 mg, 0.36 mmol) as reagent at 70°C for 48 hours. Diastereomeric ratio 90:10 (ratio from ^{1}H NMR). Diasteromeric ratio 93:7 (ratio from **^{1}H NMR**). White solid. Yield 61%. **16j** (47.8 mg, 0.11 mmol), **16j'** (46.3 mg, 0.11 mmol). Eluent: gradient hexane/ethyl acetate **16j** and **16j'** were separated by chromatography. **16j**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 – 6.99 (m, 7H), 6.63 – 6.60 (m, 3H), 4.21 (t, *J* = 6.9 Hz, 1H), 3.81 (t, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.72 – 3.65 (m, 2H), 3.33 (dd, *J* = 11.3, 6.4 Hz, 1H), 3.27 (dd, *J* = 10.6, 7.7 Hz, 1H), 3.18 (d, *J* = 16.7 Hz, 1H), 3.09 (d, *J* = 16.7 Hz, 1H), 2.92 (d, *J* = 16.6 Hz, 1H), 2.72 (d, *J* = 16.6, 1H), 2.72 – 2.62 (m, 1H), 2.61 (ddd, *J* = 15.3, 10.7, 5.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 140.7, 138.1, 135.6, 133.0, 128.2, 127.6, 127.4, 126.4, 126.3, 70.2, 70.0, 58.3, 52.8, 52.7, 50.0, 48.4, 45.8, 42.2, 41.6. **HRMS** calcd for $C_{27}H_{28}NaO_5$ ($[M+Na]^+$) 455.1838, found 455.1839; **16j': ^{1}H NMR** (400 MHz,

$CDCl_3$) δ 6.96 – 7.12 (m, 7H), 6.72 – 6.55 (m, 3H), 4.79 – 4.78 (m, 2H), 4.45 – 4.35 (m, 2H), 3.79 – 3.67 (m, 1H), 3.73 (s, 3H) 3.67 (s, 3H), 3.26 (dd, *J* = 10.9, 6.2 Hz, 1H), 2.81 (dd, *J* = 12.6, 5.9 Hz, 1H), 2.45 – 2.30 (m, 3H), 1.95 (t, *J* = 12.4 Hz, 1H), 1.55 (t, *J* = 12.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7, 140.4, 138.0, 134.8, 134.2, 128.7, 126.4, 126.1, 76.3, 75.6, 58.5, 52.8, 52.7, 50.9, 47.0, 43.0, 42.3, 37.5, 37.3. **HRMS** calcd for $C_{27}H_{28}NaO_5$ ($[M+Na]^+$) 455.1832, found 455.1832

(3a*S*,4*R*,5*R*,8b*R*)-4,5-diphenyl-7-tosyl-3,3a,4,5,6,7,8,8b-octahydro-1*H*-furo[3,4-*e*]isoindole 16k and **(4*R*,5*R*,5a*S*,8a*R*)-4,5-diphenyl-7-tosyl-3,4,5,5a,6,7,8,8a-octahydro-1*H*-furo[3,4-*e*]isoindole 16k'** were synthesized following **GP-2** using **15k** (80 mg, 0.17 mmol) as reagent at 70°C for 24. Regioisomeric ratio 50:50; Diasteromeric ratio 88:12 (ratio from ^{1}H NMR). White solid. Yield 82% (65.6 mg, 0.14 mmol). Eluent: hexane/ethyl acetate gradient **16k** and **16k'** were isolated in mixture. **^{1}H NMR** (300 MHz, $CDCl_3$)δ 7.70 – 7.66 (m, 4H), 7.36 – 7.31 (m, 4H), 7.09 - 6.97 (m, 12H), 6.62 – 6.41 (m, 8H), 4.70 (s, 2H), 4.44 – 4.30 (m, 2H), 4.23 – 4.22 (m, 2H), 4.18 - 4.13 (m, 1H), 3.91 – 3.88 (m, 2H), 3.82 – 3.70 (m, 2H), 3.63 – 3.53 (m, 3H), 3.40 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.31 – 3.16 (m, 4H), 2.70 (t, *J* = 10.5 Hz, 1H), 2.59 – 2.52 (m, 2H), 2.48 (s, 3H), 2.45 (s, 3H), 2.37 – 2.26 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.5, 143.4, 139.9, 139.3, 137.2, 137.1, 135.5, 134.6, 134.1, 133.9, 132.0, 131.2, 129.8, 129.7, 128.3, 128.1, 127.8, 127.7, 127.6, 127.6, 127.5, 127.2, 126.7, 126.7, 126.6, 126.5, 76.2, 75.3, 69.9, 69.4, 55.9, 55.4, 50.9, 50.7, 48.6, 48.2, 48.1, 46.6, 44.1, 42.2, 42.1, 41.4, 21.6, 21.6. **HRMS** calcd for $C_{29}H_{20}KNO_3S$ ($[M+K]^+$) 510.1507, found 510.1506. Vapour diffusion (hexane/ethyl acetate) allowed to recover pure crystals of **16k'**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.15 – 6.96 (m, 6H), 6.49 (d, *J* = 7.2 Hz, 4H), 4.76 – 4.61 (m, 2H), 4.47 – 4.24 (m, 2H), 3.76

(dd, *J* = 9.2, 6.9 Hz, 1H), 3.62 (br d, *J* = 6.2 Hz, 1H), 3.40 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.25 – 3.19 (m, 1H), 3.18 (dd, *J* = 10.2, 6.2 Hz, 1H), 2.70 (t, *J* = Hz, 1H), 2.45 (s, 3H), 2.35 (m, 1H), 2.29 (qd, *J* = 10.8, 6.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5, 139.4, 137.2, 135.6, 134.7, 132.1, 129.7, 128.3, 127.8, 127.6, 127.3, 126.8, 126.7, 76.3, 75.3, 50.9, 50.8, 48.7, 46.7, 42.2, 41.4, 21.6.

(*Z*)-3-benzylidene-4-methylenetetrahydrofuran 12da was observed following **GP-1** through **^{1}H NMR** (400 MHz) in benzene-d_6 yield 75% using Complex **A** (1 mg, 0.62 μmol, 1%mol) at 45°C for 14 hours employing **11d** as substrate (11 mg, 0.06 mmol, 1 equiv.) and glacial acetic acid (3.5 μL, 0.06 mmol. 1 equiv.). Spectroscopic data correspond to literature reference. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.13 – 6.95 (m, 5H), 6.75 (t, *J* = 2.6 Hz, 1H), 5.31 (t, *J* = 2.5 Hz, 1H), 4.68 (t, *J* = 2.3 Hz, 1H), 4.65 (d, *J* = 2.5 Hz, 2H), 4.33 (t, *J* = 2.3 Hz, 2H, H2). **^{13}C NMR** (101 MHz, C_6D_6): δ 146.8, 138.2, 137.3, 129.0, 128.8, 127.4, 119.1, 101.1, 71.9, 71.9.

4-Phenylanthra[2,3-*c*]furan-5,10(1*H*,3*H*)-dione 12db. Pale yellow solid. Yield 31% (19 mg, 0.058 mmol). Eluent: hexane/diethylether/ethylacetate 8:2:1 was synthesized following general procedure **GP-1** at 45°C for 16 hours using **11d** as substrate (52 mg, 0.3 mmol, 1 equiv.). Upon full conversion of **11d**, naphthoquinone (47.5 mg, 0.3 mmol, 1 equiv.) and an oxygen balloon were sequentially added and the solution was kept under stirring at 45 °C for 24 hours. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 4.7,1.8 Hz, 1H), 8.28 (s, 1H), 8.10 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.76 (td, *J* = 7.3, 1.6 Hz, 1H), 7.73 (td, *J* = 7.3, 1.6 Hz, 1H), 7.51- 7.40 (m, 3H), 7.20 (dd, *J* = 7.9, 1.4 Hz, 2H), 5.29 (s, 2H), 4.85 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 183.2, 183.1, 146.7, 144.7, 139.5, 138.0, 135.1, 134.4, 134.2, 133.7, 132.7, 130.3, 128.6, 127.5, 127.4, 126.8, 119.8, 74.1, 73.6. **HRMS** calcd for $C_{22}H_{14}NaO_3$ ([M+Na]+) 349.0835, found 349.0835

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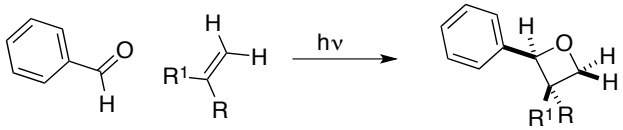
6 Introduction to photocatalysis

Visible light mediated reactions are receiving a remarkable attention in the last years among catalysed procedures. One of the basic aims in the field of catalysis is the activation of small molecules. A master example comes once more from nature, which uses light in the photosynthesis of carbohydrates from carbon dioxide and water. The importance of visible light mediated reactions resides in the possibility to use the energy of photons for synthetic purposes. Moreover, light is the most largely available and cheaper energy source. The combination of light with catalysts is an attractive tool for developing efficient and selective chemical transformations. [198]

The beginning of the studies in light interaction with matter came from 1772 when Scheele discovered the effect of light on $AgCl_2$ and that allowed the development of photography during the 1780s. The first investigation about the interactions between organic molecules and light was reported by Grotthus in 1820. He understood that reactions could proceed with light and molecules could adsorb the light. In 1795, Trommsdortff observed the dimerization of (-) α-santonin, whose crystals turned yellow when exposed to sunlight, but only in 2007 the reaction was completely understood. [199] In the later 1850s the difference between light absorption and light-mediated reactions started to be understood. Indeed, light mediate reactions are a consequence of light adsorption. During the beginning of the XIX century, Einstein and Jablonski described accurately the interaction of light and matter. In the second part of nineteenth century, Paternò and Ciamician built the basis of photochemistry. The research of Ciamician led to the discovery of several new reactions, among them the photoreduction of aldehydes, ketones,



Scheme 38 Example of Paternò- Büchi reaction

quinines, and nitro compounds as well as the photodimerization and cycloaddition of olefins. Paternò and Chieffi in 1909 discovered the formation of oxetane, a four-member ring formed from benzaldehyde and 2-methyl-2-butene exposed to sunlight, but the structure was confirmed only in 1954 by Büchi. This reaction becomes known as the Paternò-Büchi reaction. [200] Some further important studies were reported by Schönberg. His studies included the reaction of aldehydes with phenanthraquinoneimine to form 2-hydroxy-2,3-dihydrophenanthroxazole derivatives, the photopolymerization of coumarins and the photoaddition and photoreduction of aromatic ketones. Starting from the 1930s, photochemical heterogeneous transformations were described, mostly using TiO_2. In the last twenty years, this concept was applied in widespread fields like water splitting, carbon dioxide reduction and development of solar cell materials. However, only in the last decades photocatalysis became a hot topic in organic synthesis. [201]

In the field of organic photocatalytic transformations, chemists found the important advantage of using milder reaction conditions compared to classic synthetic routes. One of the most important issue to deal with is represented by the light adsorption of organic molecules. Indeed, most organic molecules are not able to adsorb visible light. For this reason, photocatalytic transformations need a light-adsorbent photocatalyst.

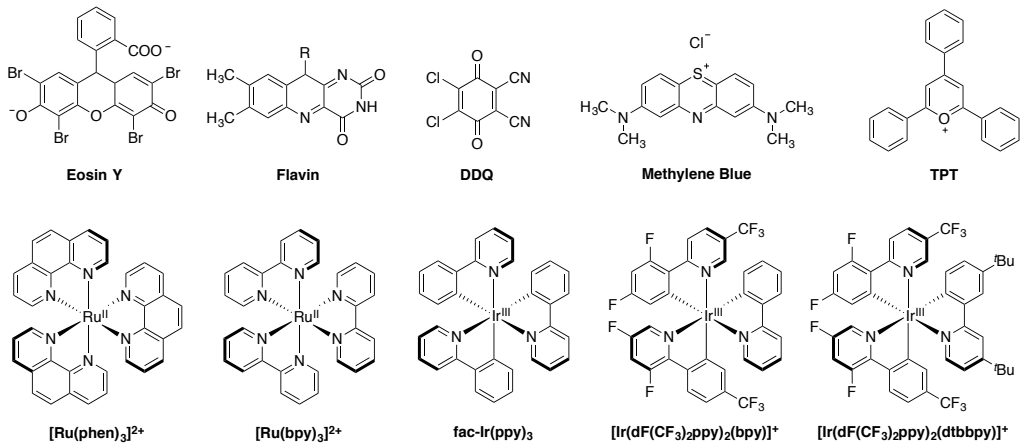


Figure 9 Selected examples of photocatalyst

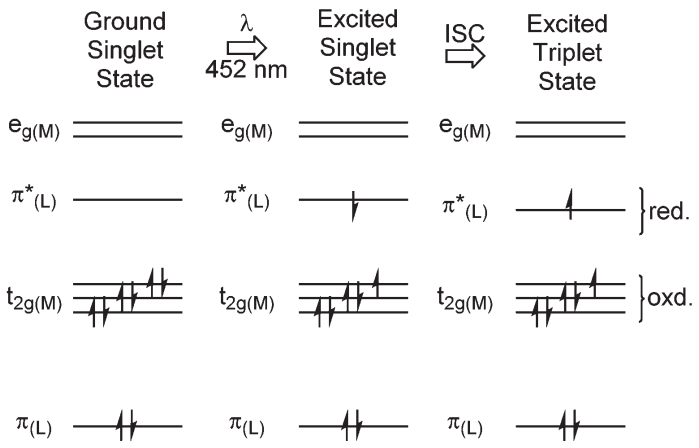
This chemical species can adsorb energy form the appropriate photons and transfer it to organic molecules. Different types of photocatalysts can be employed, such as transition metal complexes or organic dyes. However, the long lifetime of transition-metal photocatalysts excited states, coupled with their higher chemical stability, often ensures an edge over organic ones in promoting chemical transformations. A wide range of ruthenium and iridium polypyridyl complexes as well as different types of organic catalysts are already known. [202]

The ability to tune the electronical properties of the catalyst significantly extends the repertoire of the transformations that can be performed. The most important features of photocatalysts are the wavelength of their adsorption and the redox potentials of their higher multiplicity spin states. The choice of the catalyst needs to be carefully balanced based on the redox potential of substrates. [203]

Small organic molecules can be activated by three reaction pathways, depending on the photocatalyst employed, the nature of substrate and the reaction conditions. These pathways can be divided into two photoredox and one

photosensitizer mechanisms. Here will be described these general mechanisms using a transition metal complexes. [201,204]

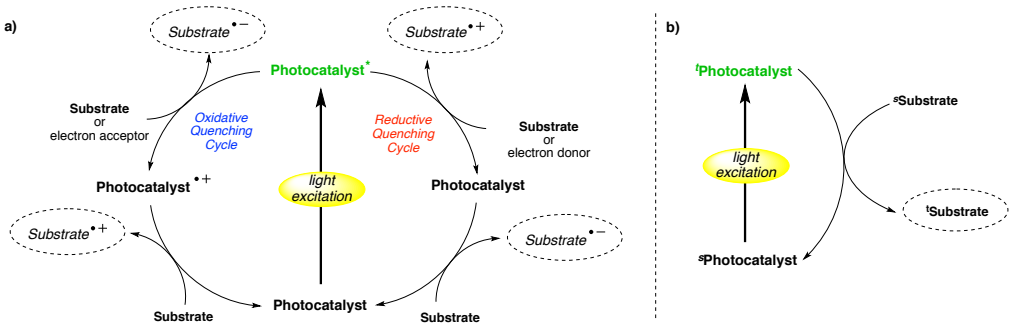
Photocatalysts through absorption of the correct photons promote an electron from a *d*-orbital of the metal to empty orbital of the ligand (metal-to-ligand charge transfer MLCT), yielding a singlet excited state. Rapid intersystem crossing (ISC) leads to a long-living triplet state. This triplet state can serve as an oxidant (through its partially empty SOMO-1 orbital) or a reductant (through its higher energy SOMO), and as an energy transfer agent. [204] Photocatalysts in this configuration present therefore a redox amphoterism. In fact, the excited state is a much more potent electron donor than the complex ground-state and at the same time, it is a much stronger oxidant too. For these reasons, photocatalysts can behave either as oxidant or as reductant through singlet electron transfer (SET) reactions.



Scheme 39 Orbital energy level of $[Ru(bpy)_3]^{2+}$

In the two photoredox pathways, the single electron transfer can then follow two reaction manifolds, depending on the presence of an oxidative or a reductive quencher to regenerate the ground state of the catalyst.

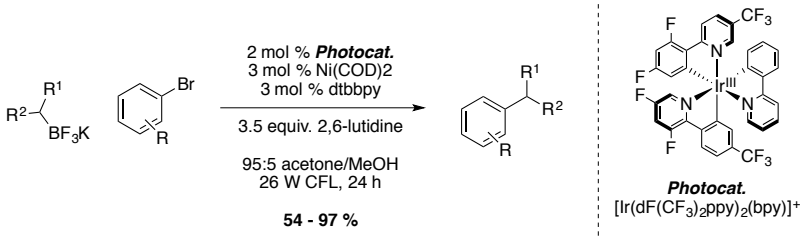
The activation of organic molecules can also proceed via energy transfer. In this case, the triplet state of the photocatalyst can transfer its energy to the substrate, which has to own a suitable singlet/triplet gap. The catalyst comes back to the ground state and the triplet excited substrate is now able to react.
The important applications of photocatalysis show the possibility to reduce the severity of reaction conditions and apply this strategy to trigger very mild cross-couplings, α-amino functionalization, cycloadditions, ATRA and fluorinations.



Scheme 40 Mechanism of photocatalyzed reaction; **a)** Photoredox pathway; **b)** Photosensitizer pathway

6.1 Photocatalyzed C-C and C-N bond formation

The development of new methods to form C-C and C-N carbon bonds have attracted much interest in the community of chemists and many photocatalyzed reactions have been developed. The formation of carbon-carbon bonds is largely achieved by cross-coupling palladium methodologies. These methods as already mentioned require a stoichiometric amount of organometallic reagent, such as zinc, lithium, tin ecc. An attractive photocatalytic alternative was discovered by Molander in 2014. He reported a Suzuky-Miyaura cross-coupling catalysed by nickel and an iridium photocatalyst using trifluroborates and arylbromides. [205] In this reaction, photocatalyzed oxidation of trifluroborates leads to the formation of an alkyl radical that can add on an arylnickel complex. The subsequent reductive elimination yields the product. Other important examples were reported by Fensterbank, Molander and MacMillan. These examples uses a prefunctionalized silicium substrate, which turn hypervalent throughout the sequence. [206–208] Recently, Molander reported the first C-H activation of THF to arylate its C-2 position. [209] Experimental evidences showed that the photocatalyst produce a Ni (III) species that is able to activate the C-H bond of THF. This method permits the coupling of a large palette of aryl and heteroaryl bromides and can be compared to classical arylation methodologies.



Scheme 41 Example of photocatalyzed aromatic arylation

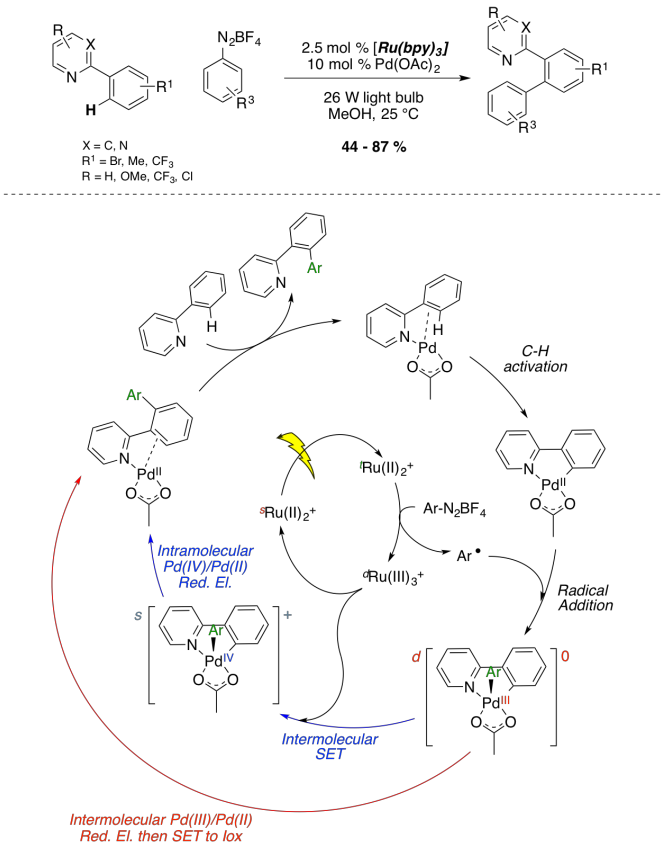
Typically, palladium cross-coupling reactions involve Csp2-Csp2 bond formations. These methodologies often require heating. For this reason,

photocatalytic processes can be a smart strategy to trigger conceptually similar reactions under milder conditions. As reported 30 years ago by Cano-Yelo and Deronzier, aryldiazonium salts are useful reagents in photocatalytic reactions. In fact, they can easily undergo to SET mechanism to generate an aryl radical reagent.

An interesting example of C-H bond functionalization, which employs a join photo/palladium catalysis was reported by Sanford in 2011. [210] In this work she proposed the formation under visible light of an aryl radical through a SET mechanism. Then, the aryl radical add on a Pd(II) metallacycle to give a radical Pd(III) intermediate, which undergoes oxidation to Pd(IV) with the concomitant regeneration of the Ru complex ground state. Reductive elimination from the Pd(IV) complex produces the product and regenerates the Pd(II).

A more favorable reaction mechanism was later found by our group (right part of Scheme 42). [211]

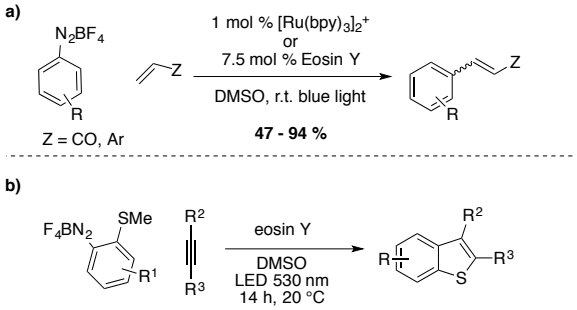
Meerwein in 1939 reported the arylation of alkenes, alkynes and enones employing diaryldiazonium salt. This



Scheme 42 Example of C-H photocatalyzed activation and mechanism

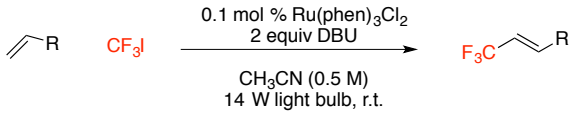
methodology suffers from low yields and the use of ionic liquid chlorinated agents to promote the reaction. The reaction is furthermore limited to the use of activated compounds such as coumarins, quinones, stryrenes and phenylacetylenes. An important improvement was recently reported by Konig in 2012. [212]

An example of photocatalysed synthesis of heterocycles was reported in 2012 by Konig. [213] This paper illustrated the annulation of *o*-thiomethylarenediazonium salts with internal alkynes in presence of eosin Y, an organic dye, as photocatalyst. A large variety of alkynes and arenes is used to give the corresponding benzothiophenes.



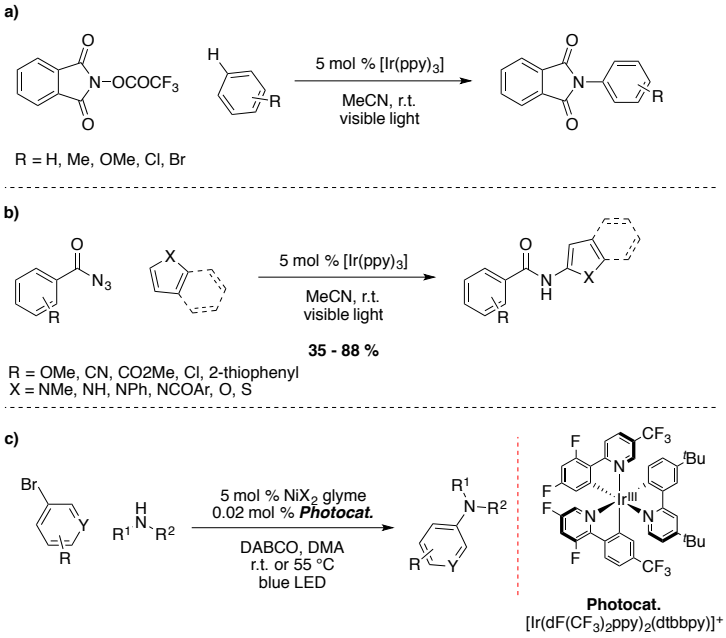
Scheme 43 Selected examples of photocatalyzed arylation

A powerful photocatalytic synthetic method for the formation of carbon-carbon bond is represented by atom transfer radical additions (ATRA). In the classical mechanism, homolytic cleavage of R-X bond generates an alkyl radical, R•, which can undergo chain reactions. The original reaction was conducted under a thermal regime, employing temperature between 100 and 150 °C. These conditions lead frequently to a large amount of by-products.



Scheme 44 Examples of trifluoromethylation of alkenes

Photocatalysed versions can be performed at room temperature, in order to minimize the formation of side products. ATRA reactions can be applied for the synthesis of alkenes and for cyclization reactions.



Scheme 40 Selected examples of photocatalyzed a) and b) Amidazion reaction, c) amination reaction

Alkenes are one of the most important class of organic molecules and a considerable number of methods for their preparation is already known, such as palladium cross-couplings, Wittig reactions and alkenes metatheses. Photocatalyzed approaches are widely use for the synthesis of CF_3-conteining compounds. Cho reported the trifluoromethylation of alkenes with CF_3I under visible light using a ruthenium photocatalyst combined with DBU, via an ATRA mechanism followed by elimination of iodine. [214]

As already discussed above, carbon-heteroatom bond formation represents an important goal for chemists. This section presents selected examples of carbon-

nitrogen bond formation. Recently photocatalytic approaches were reported as an efficient alternative to Buchlwald-Hartwig and Ullman reactions. Pioneering works on photocatalytic aminations were addressed by Skell. [215] Later an important paper was reported by Stanford in 2014, in which she reported the amination of aromatics and heteroaromatic arenes employing N-trifluoromethylacyloxyphthalimide. [216] Konig in 2015 reported the visible light mediated C-H amidation of heteroarenes with benzoyl azides. [217] The reaction proceeds with good yields employing either electron withdrawing and donating groups.

Recently, Buchwald and MacMillan reported an important step forward in cross-coupling amination reactions. [218] In this paper they reported the reaction of aryl halides with alkyl-substituted primary and secondary amines using a joint $NiBr_2$/ iridium complex catalytic system. They described accurately the reaction mechanism. The single electron transfer within a Ni(II)-amino complex intermediate and the photocatalyst generates a Ni(III) complex that undergoes fast reductive elimination to yield the desired product. The key step in the photocatalyzed approach is represented by the destabilization of nickel amino complex to promote the reductive elimination.

6.2 Photocatalyzed cycloaddition

One of the most widely known application of photocatalysis is certainly in cycloaddition reactions. Due to its ability of assembling complex molecules with high stereoselectivity, cycloadditions are one of the most used and studied reactions in organic synthesis. The rules of these transformations based on the conservation of orbital symmetry and on the HOMO/LUMO energy gaps were described by Woodward and Hoffmann, as a smart tool to rationalize observed reactivities. [219,220] Cycloadditions can proceed thermally or photochemically, roughly depending on orbital symmetry. If the symmetry of the involved orbitals is correct to ensure overlap, the energy gap between the HOMO and the LUMO of the reactants has to match in order to observe the cyclization. For these reasons, often the use of a catalyst is required. The most frequent cycloadditions are [4+2], [3+2] and [2+2] reactions.

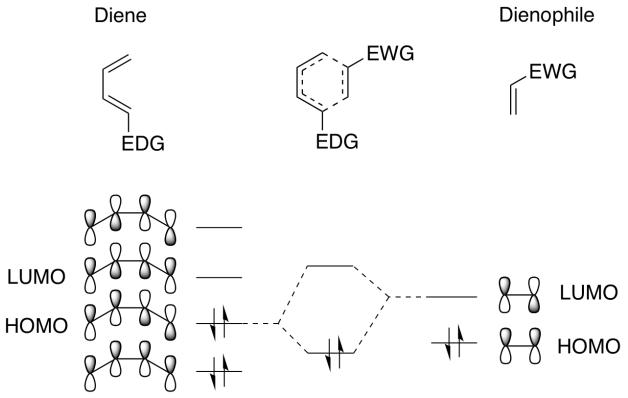
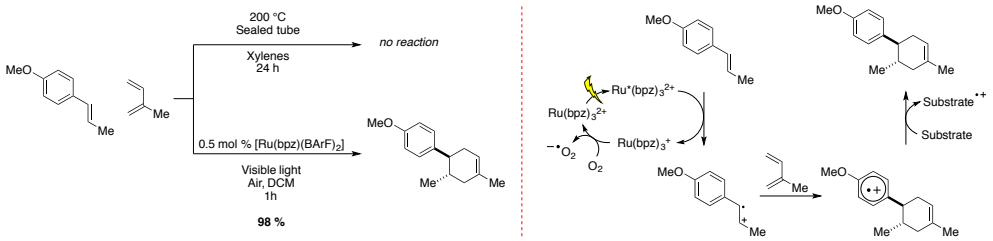


Figure 10 Molecular orbital in [4+2] cycloaddition

The [4+2] Diels-Alder reaction proceeds between a dienophile and a diene. The reduction of the energy gap between the HOMO and the LUMO of the two partner can need different types of catalysts. [157]

One of the most brilliant examples of photocatalyzed [4+2] cycloaddition was reported by Yoon in 2011. [189] In this paper was illustrated how the photocatalysis can be complementary to classical heating strategies. The Diels-Alder reaction studied did not proceed by thermal conditions because of the high-

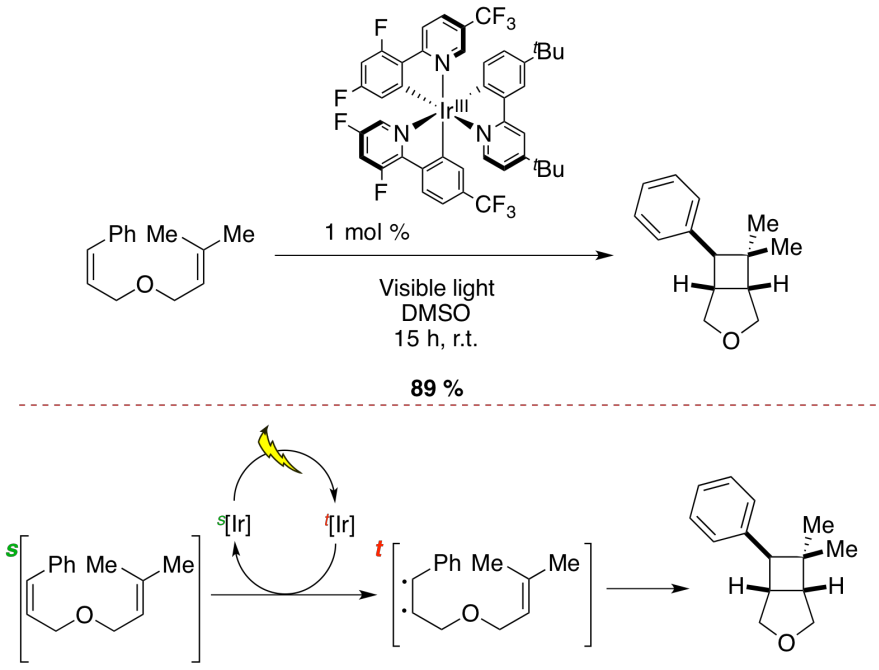
energy gap between the LUMO and the HOMO of the two reagents. However, the reaction can be achieved at r.t. introducing a suitable photoredox catalyst able to oxidize the electron rich dienophile The triplet state of the photocatalyst oxidize the styrene to the corresponding radical cation thanks to the presence of the methoxy substituent that significantly lowers its potential. This sunk in turn the energy level of its LUMO, enabling a smooth reaction with the electron rich isoprene partner and thus forming a six-membered ring radical cation intermediate. Reduction of the latter regenerates the catalyst and yields the product.



Scheme 41 Selected example of photocatalyzed [4+2] cycloaddition reaction and

The [2+2] reactions are equally important in organic synthesis, enabling to access cyclobutane motifs. These reaction cannot occur under thermal conditions, and the use of (UV) light or of a catalyst is therefore indispensable. A Lewis acid catalysed reaction was reported in 2015 by Chirik, in which the dimerization of alkenes was catalysed by an Iron(0) complex. [221] A photocatalyzed [2+2] reaction approach was reported by Pranday and later by Yoon. [222–224] In this case, Yoon in analogy with the [4+2] reaction, reported one-electro reduction of styrene carried out by a photocatalyst affording a radical cation that undergoes to [2+2] cycloaddition. However, activation of non-conjugated alkenes and of electron-poor styrenes remains so far an open issue.

An important alternative to these examples of [2+2] cycloadditions is represented by reactions occurring via energy transfer. Iridium based photocatalysts are known to be able to transfer the energy as their triplet state to substrates having a relatively accessible triplet state. Yoon reported the intramolecular cycloaddition of a diene bearing a styryl arm. [225] Later Wu and Reiser applied this mechanism to intermolecular [2+2] homocoupling cycloadditions of styrenes, cinnamates and chalcones as well as to the heterocoupling of cinnamates with 1,1-diarylethylenes. [226,227]



Scheme 42 Selected example of [2+2] photocatalyzed cycloadddion via energy transfer mechanism

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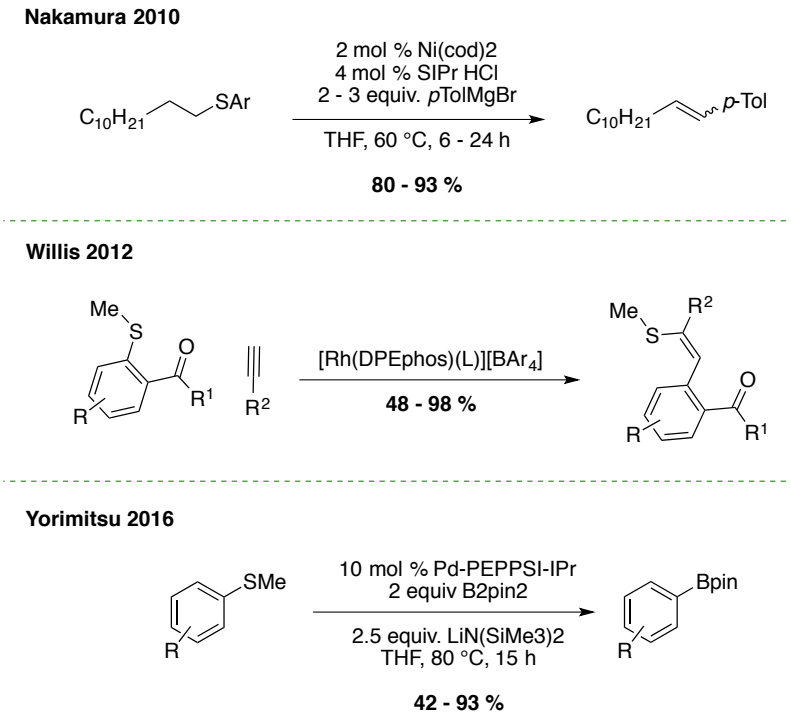
7 Visible-Light C−C and C−N Bond Formation by C−S Bond Cleavage

From this caption: Matteo Lanzi, Jérémy Merad, Dina Boyarskaya, Giovanni Maestri, Clémence Allain and Géraldine Masson, *Org. Lett.* **2018**, *20*, 5247 − 5250

7.1 Introduction

In the last decades, transition metal catalysed cross-coupling is the main synthetic strategy in the field of C-C and C-heteroatom bond formation. Most of these reactions employ aryl halides as electrophilic coupling partners to perform the cross-coupling with nucleophilic organometallic reagents to form the new C–C bond. Few works have been reported using sulfides as electrophiles. [228] Sulphides are emerging as important alternative in cross-coupling reactions. [229,230] Transition metal C-S bond cleavage protocols are already reported employing allylic sulfides, thiocyanates, thioesters, thiocarbamates, thioalkynes, thiranes and thiophenes. However, most of these approaches display a narrow scope due to the ability of the Lewis basic sulfur atom to poison electron-deficient catalysts. [231–233]

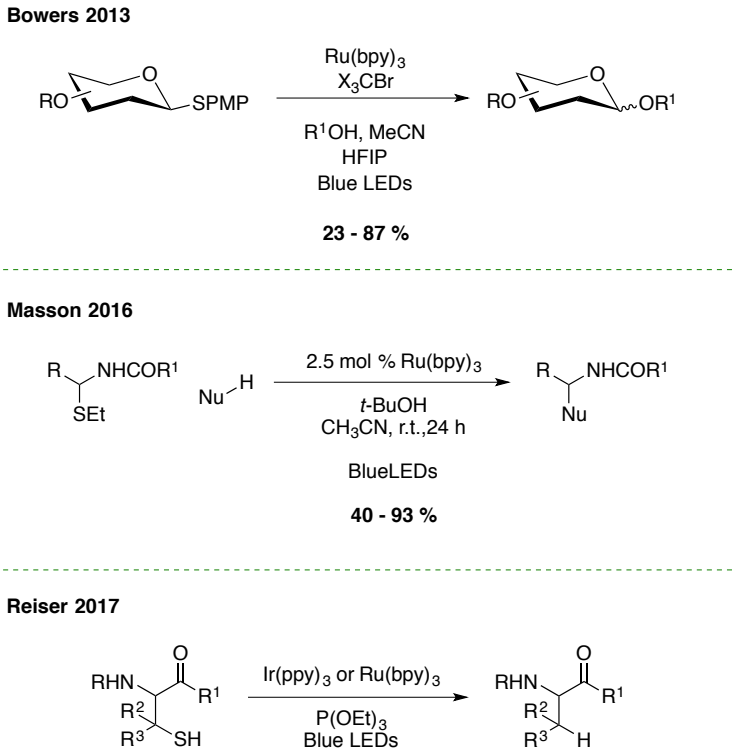
The first example of palladium catalysed cross-coupling that engage C-S bond cleavage was reported in 2010 by Liebeskind–Srogl employing thioesters and organoboronic acids with equimolar copper and without additional bases. [234] Nakamura reported an alternative nickel cross-coupling method using alkyl sulfides with Grignard reagents.[235] The direct activation of simple aryl sulfides was reported by Willis using terminal alkynes in a rhodium catalysed carbothiolation reaction. [236] Recently, Yorimitsu proposed an alternative borylation coupling using aryl sulfides and diboranes. [237]



Scheme 43 Selected examples of C-S bond cleavage transition metal catalysed

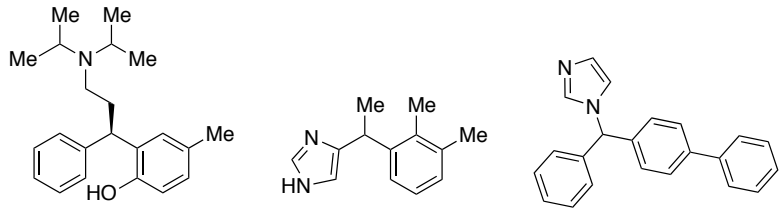
Selective oxidation of thioethers can be efficiently ensured by a photoredox catalysis. It does not involve coordination of their sulfur atom to the catalyst, which poison transition metal complexes. This approach has been extensively studied to synthesize sulfones and sulfoxides, mainly employing organic photocatalysts. [238–244]

Howereve, the selective oxidation of thioethers remains a surprisingly underexplored strategy. Bowers reported in 2013 the first example of a selective photocatalyzed oxidation of a thioether. [245] He describe O-glycosylation using an iridium complex as catalyst.



Scheme 44: Selected examples of photocatalyzed C-S bond cleavage

Later, Masson reported an innovative synthesis of N-carbamoyl α,α-disubstituted amines from readily available α-amidosulfides under mild conditions. [246,247] This methodology involves the C−S bond cleavag using a ruthenium photocatalyst. More recently, photoredox-catalised C-S bond cleavage was applied to desulfurization reactions. Reiser in 2017 reported the desulfurization of cysteine in presence of a ruthenium complex, which occurs using a surprisingly low catalyst loading of 0.01 mol%. [248]



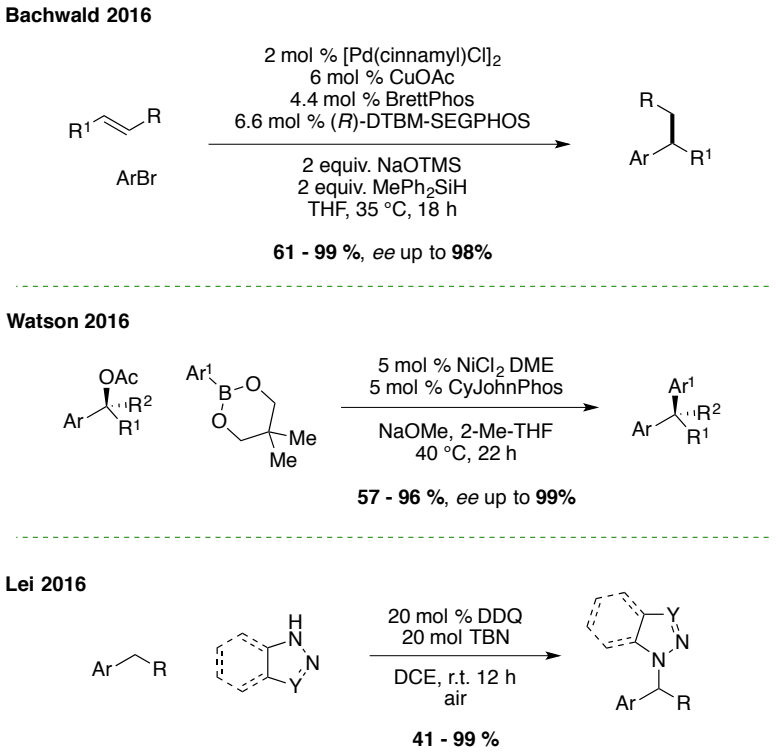
Tolterodine
Urinary incontinence

Medetomidine
Analgesic

Bifonazole
Antifungal

Figure 11 Selected examples of di- and tri arylmethanes

Di- and triarylalkanes are found in numerous pharmaceuticals and natural products. [249,250] The main strategies to synthesize them use cross-coupling reactions. [251] Recently, stereoselective approaches too were reported. [252–254] In 2016, Buchwald reported an interesting enantioselective palladium catalysed approach that involves the hydroarylation of a double bond. [255] This protocol uses enantio enriched phosphines to achieve a large family of diarylmethanes with high stereocontrol. Watson described a stereospecific Suzuky-Miyaura cross-coupling using nickel catalysis. [256] He illustrated the formation of enantioenriched quaternary carbons via electrophilic allylic addition.

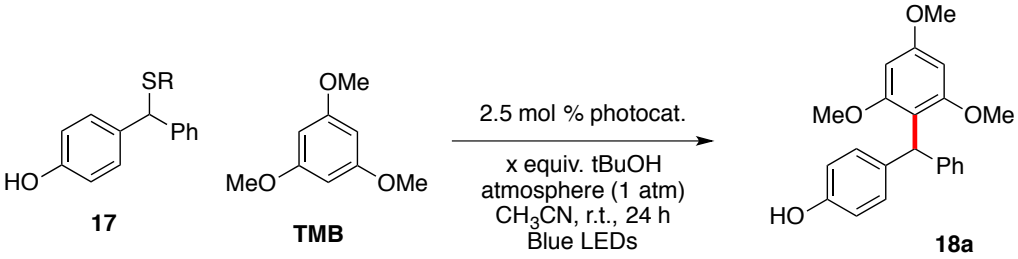


Scheme 45 Selected examples of recent methodology for the sinthesis of di- and triarylalkanes

More recently an aerobic metal-free approach was reported by Lei. [257] This reaction utilized a catalytic amount of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) and *tert*-butyl nitrite for the direct oxidation of benzylic C-H bonds to achieve di- and triarylmethanes.

7.2 Result and discussion

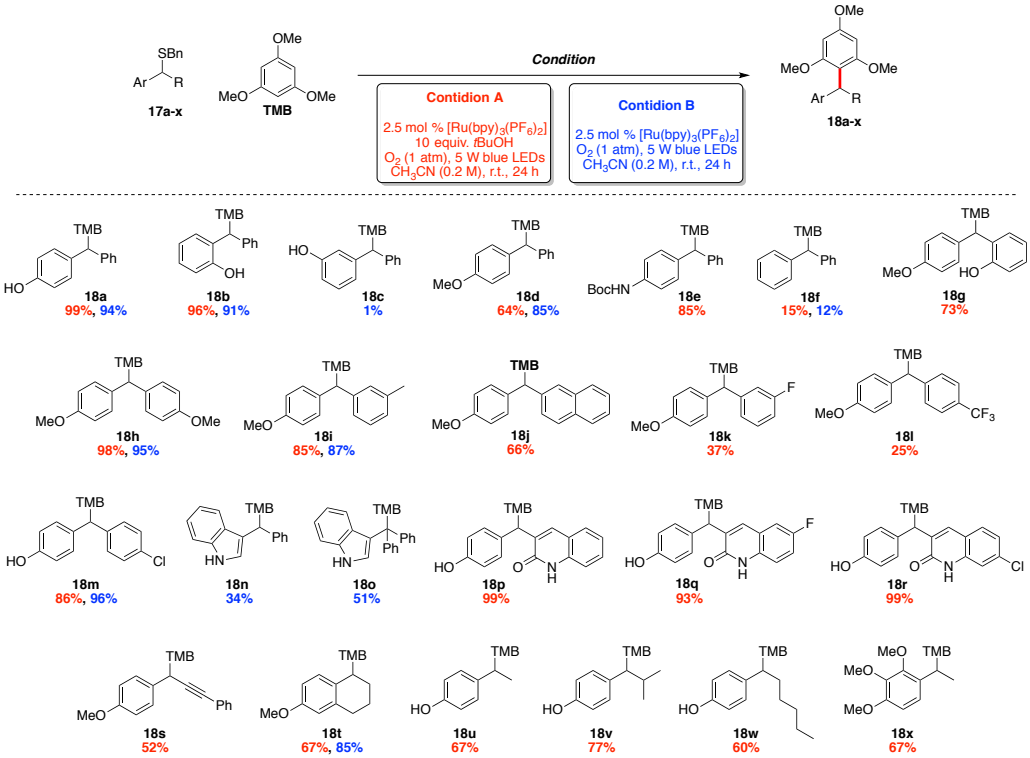
The photocatalyzed oxidative C−S bond cleavage of benzyl thioethers is a potential soft route to access triarylmethanes. Based on recent works of the Masson group, we initially attempted to functionalize 4-ethylthio(phenylmethyl)phenol **17a** with 1,3,5- trimethoxybenzene (TMB) in the presence of *fac*-Ir(ppy)$_3$ in acetonitrile/t-BuOH (8:2, v/v) under visible light irradiation (5 W blue LEDs) with molecular oxygen as an oxidant.



Entry	R	Cat.	Atmosphere (1 atm)	x equiv. *t*BuOH	Yield 18a (%)[b]
1	Bn	*fac*-Ir(ppy)$_3$	O_2	10	83
2	Bn	Eosin Y	O_2	10	67
3	Bn	[Ru(bpy)$_3$(PF$_6$)$_2$]	O_2	10	99
4	Ph	[Ru(bpy)$_3$(PF$_6$)$_2$]	O_2	10	56
5	Et	[Ru(bpy)$_3$(PF$_6$)$_2$]	O_2	10	84
6	tBu	[Ru(bpy)$_3$(PF$_6$)$_2$]	O_2	10	71
7	Bn	[Ru(bpy)$_3$(PF$_6$)$_2$]	O_2	0	94
8	Bn	[Ru(bpy)$_3$(PF$_6$)$_2$]	O_2	0	94[c]
9	Bn	[Ru(bpy)$_3$(PF$_6$)$_2$]	O_2	0	0[d]
10	Bn	[Ru(bpy)$_3$(PF$_6$)$_2$]	air	0	83
11	Bn	[Ru(bpy)$_3$(PF$_6$)$_2$]	argon	0	14
12	Bn	--	O_2	0	11

[a] General conditions: **17a** (0.10 mmol, 1 equiv), TMB (0.15 mmol), photocat. (2.5 mol %), t-BuOH (0 or 10 equiv) in CH_3CN (0.5 mL) irradiated with 5 W blue LEDs at rt for 24 h. [b] Isolated yields. [c] Reaction performed on a 1 mmol scale (of **17a**). [d] Reaction performed in the dark.

At the beginning, we tested different photocatalysts. Ruthenium photocatalyst showed the best activity, isolating the desired triarylmethane derivative **18a** in almost quantitative yield after 24 h (entries 1–3). The nature of the thioether moiety has demonstrated a crucial influence on the reaction outcome. Indeed, when R is a tert-butyl or a phenyl group, the substitution efficiency was significantly decreased. However, *S*-benzyl derivative afforded **18a** in a nearly quantitative yield (entries 3–6). In contrast to previous studies, the presence of *t*-BuOH does not have a prominent effect when **17a** and TMB ware the reaction partners. Pleasingly, the reaction can be performed on a 1 mmol scale without any change in rates or yields (entry 8). Control experiments showed that the reaction failed to proceed in the absence of light (entry 9). A slower substitution was observed in an open-air flask (entry 10), highlighting the positive effect of the concentration of O_2 on the reaction rate. This observation was supported by a dramatic conversion drop when the arylation was performed under an argon atmosphere (entry 11). Then, we found that when the flask was irradiated for 24 h in the absence of catalyst, **18a** was isolated in 11% yield (entry 12). This striking observation suggested a potential, although poorly efficient, direct photoactivation of substrate **17a** under blue LED irradiation.

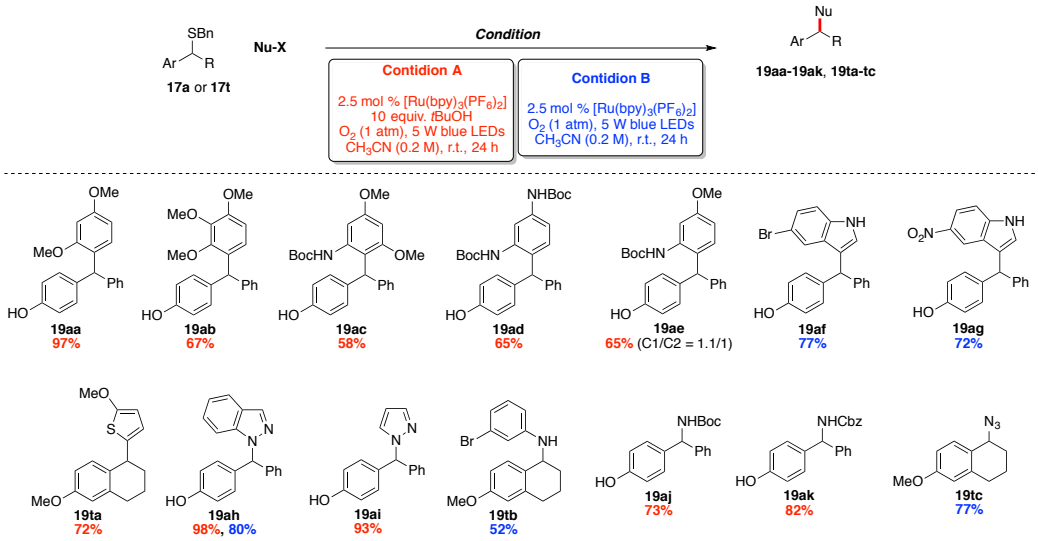


Scheme 46 Reaction scope of thioehers

With the optimized reaction conditions in hands, the scope of the photocatalyzed arylation of benzylthioethers with TMB was then explored.

Diarylmethanes bearing strong donating substituents provided triarylmethanes with good to excellent yields. In contrast, products **18c** and **18f** were isolated in 1% and 15% yields, respectively. In the synthesis of **18c** and **18f**, sulfoxides arising were identified as the main reaction products. A similar trend was brought to light for anisole derivatives, since the photocatalytic arylation was found efficient for electron-donating substituents (**18g - j**). On the other hand, the presence of electron-withdrawing groups as *m*-F and *p*-CF_3 resulted in the formation of products **18k** and **18l** in low yields. The reaction proceeded smoothly when combining highly electron-rich phenols with electron-poor arenes (**18m**).

Heteroaromatic substituents such as 3-indolyl or 3-quinolinonyl groups were also competent reaction partners, delivering products (**18n − r**) that have potential applications in medicinal chemistry. Extension of this novel photocatalyzed protocol to diverse secondary benzylic thioethers was also successful, providing efficient access to biologically relevant diarylalkanes. The arylation can be efficiently applied to propargylic thioethers as well as cyclic and acyclic benzylic substrates **18s − w**. Additionally, this transformation provides an efficient route to anticancer isoerianin analogue **18x**. [258] It has to be noticed that the presence of *t*-BuOH can have a slight impact on the reaction efficiency but we were so fa unable to establish a clear relationship with the structure of the substrate.

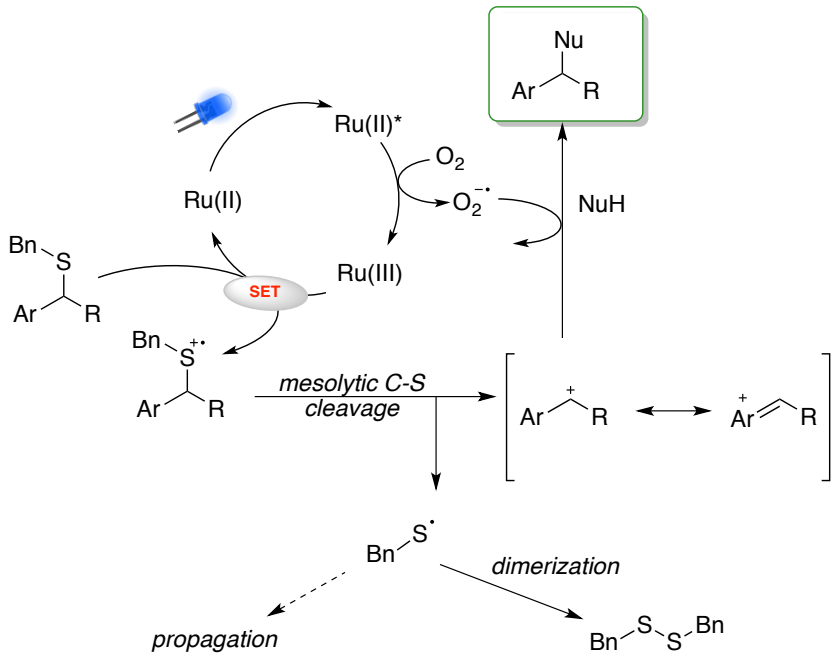


Scheme 47 Reaction scope of nucleophiles

Encouraged by these results, we turned our efforts toward extending this protocol to other nucleophiles. Diversely substituted arenes and heteroarenes readily participated in C−C bond formation to afford the expected triarylmethanes **19aa**−**19ta** in good yields. Moreover, the construction of C−N bonds can also be achieved thanks to this method. Various azole derivatives were successfully incorporated giving rise to building blocks **19ah** and **19al** that can be found in several important drugs. [257,259–261] Nonaromatic *N*-nucleophiles such as carbamates, anilines, and azides were also found to be viable reagents (**19tb**, **19aj**, **19ak**).

To gain insight into the mechanism of the photoredox-catalyzed thioether C−S bond cleavage, we first determined the redox potential of several thioethers. Model substrate **17a** displayed an oxidation potential $E_{1/2}$= +0.85 V vs Fc/Fc^+ in CH_3CN that makes a direct SET thermodynamically unlikely from the excited stated of $[Ru(bpy)_3(PF_6)_2]$ (Ru(II)*/Ru(I): E_0= +0.37 V vs Fc/Fc^+ in CH_3CN). [262] This was confirmed by Stern−Volmer experiments in which no significant

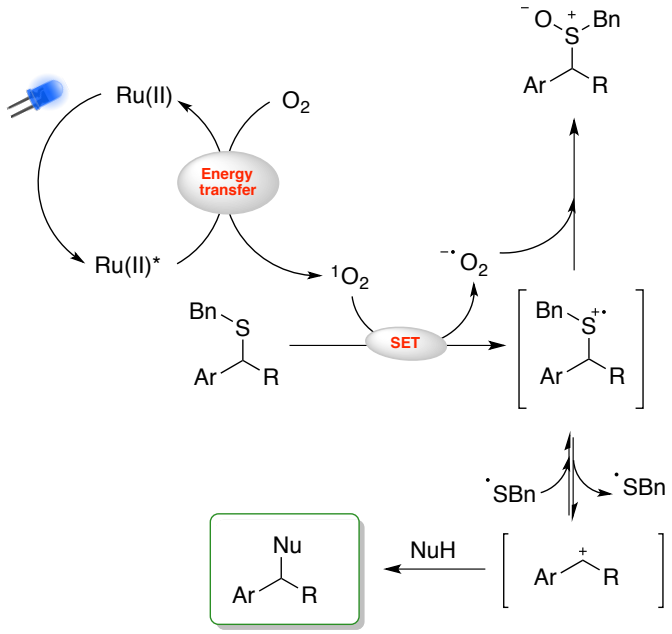
fluorescence quenching was observed in the presence of **17a** or TMB. Based on these observations and on the requirement of O_2, we assumed that Ru(III) (Ru(III)/Ru(II): E_0= +0.89 V vs Fc/Fc^+ in CH_3CN) could be the active oxidant of electron-rich substrates.



Scheme 48 Suggested mechanism for substrate with $E_{Ox1/2} \leq E_{Ru(III)/Ru(II)}$

The mesolytic cleavage of the C−S bond into a thiyl radical and a carbocation was supported by several experimental proofs. The involvement of a carbocation intermediate (S_N1-type process) is consistent with the complete loss of enantiomeric excess through the arylation of optically pure thioether **17a**. Also, the disulfide resulting from the dimerization of two thiyl radicals was isolated in 83% yield when **17a** was reacted with TMB. [263] In a final step, the addition of the nucleophile onto the carbocation could be assisted by the basic superoxide radical anion. Correlations between the Hammett parameters (σ) of aromatic substituents and the corresponding yields obtained after 24 h have highlighted a

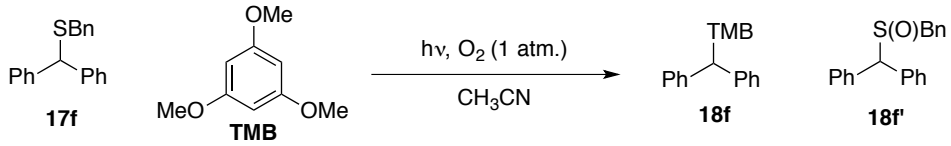
drop in yields in the presence of substituents with σ values ≥0. This could be explained by a dramatic increase in their oxidation potentials of the related substrates. The oxidation potentials of **17f** ($E_{1/2}$ = +1.18 V vs Fc/Fc^+ in CH_3N) and of **17k** ($E_{1/2}$ = +1.14 V vs Fc/Fc^+in CH_3CN) are elusive for Ru(III), suggesting that another reaction mechanism is at work in these cases.



Scheme 49 Suggestion mechanism for substrate with E_{Ox} >> $E_{Ru(III)/Ru(II)}$

In this case, sulfur oxidation could rely on the formation of singlet oxygen $^1O_2$ formed via energy transfer. [264,265] In order to shatter this main scope limitation, photocatalysts with higher oxidation potentials were tested in the arylation of **17e**. However, no significant improvement of the yield was observed. These results could be explained by a slow C−S bond cleavage because of the limited stability of the corresponding carbocation. Unfortunately, the use of alternative oxidants to prevent the formation of sulfoxide uniformly resulted in no conversion..

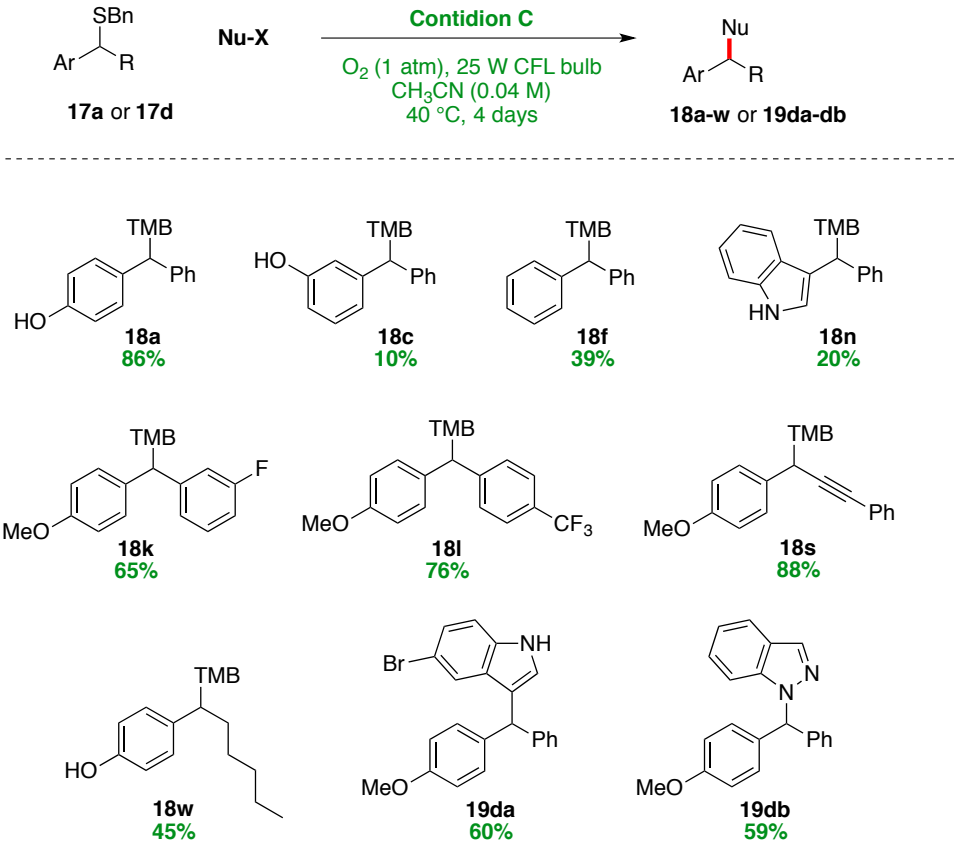
We then optimized a catalyst-free method based on the previous observation that certain benzylthioethers could be activated by light alone.



Entry	Conc. (M)	hν	Yield of 5e (%)[b]	Yield of 7e (%)[b]
1	0.2	Blue LEDs	0	0
2	0.2	25 W CFL bulb	6	0
3	0.2	λmax = 365 nm	14	36
4	0.04	25 W CFL bulb	39	0
5	0.04	25 W CFL bulb	43[c]	0

[a] General conditions: 5f (0.1 mmol, 1 equiv.), TMB (0.15 mmol, 1.5 equiv.) in CH_3CN irradiated at the specific wavelength in a reaction tube (∅ = 10 mm) over 4 days; [b] isolated yield; [c] Reaction tube (∅ = 6 mm)

We hypothesized that an appropriate choice of conditions would allow the formation of triarylalkanes while preventing competitive sulfur overoxidation. **17a** remained unreactive under 5 W blue LED irradiation. However, the use of a 25 W CFL bulb and a higher dilution enabled the formation of **18a** in 39% yield.



Scheme 50 Investigation of photocatalyst-free reaction

The synthetic potential of this new set of conditions was then explored. Electron-rich substrates underwent smooth addition to TMB, although in lower yields compared to the Ru-catalyzed process. However, the catalyst-free substitution furnishes enhanced efficiency in the case of electron-deficient substrates. Fluorinated products **18k** and **18l** were then obtained in 65% and 76% yields, respectively. This highlights the complementarity between the two methodologies described herein. Highly deactivated thioether **17c** was converted to triarylmethane **18c** in 10% yield only. The photoinduced desulfidation also turned out to be more suitable to access diarylalkyne **18s** and **18w**. Various arenes and heteroarenes can be used as the reaction partners, as demonstrated by the formation of compounds **19da** and **19db** in rather good yields. Even if the

mechanism of this transformation is not fully understood, it is expected to involve a visible-light-induced homolytic cleavage of the C−S bond. [266–269]

7.3 Conclusion

We described a visible-light photoredox catalysed synthesis of diarylalkane and triarylmethane derivatives under neutral conditions. The reported strategy relied on the oxidative weakening of sulfidic C−S bonds allowing the *in-situ* generation of the reactive carbocations. An appreciable range of substrates and nucleophiles can be engaged in this transformation that uses O_2 as oxidant. This work finally revealed the possibility of inducing homolytic C−S bonds cleavage under direct visible-light irradiation. This catalyst-free approach efficiently complemented the first methodology since it ensures the formation of C−C and C−N bonds using more electron-deficient substrates.

7.4 Experimental section

General procedure A: Benzylic alcohols synthesis: $NaBH_4$ (5.0 equiv) was slowly added onto a solution of ketone (1.0 equiv) in MeOH (0.2 M) at 0 °C. The resulting solution was then allowed to reach room temperature and stirred until complete conversion (monitored by TLC). The solvent was then removed under reduced pressure and the resulting solid was dissolved in CH_2Cl_2. This organic solution was successively washed with water and a saturated aqueous solution of NH_4Cl. The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum to afford the desired product without further purification was needed.

General procedure B: Benzylic alcohols synthesis: A solution of arylbromide (4.0 equiv) and 1,2-dibromoethane (0.05 equiv) in freshly distilled THF (2 M) was added over 30 minutes onto metal magnesium (4.0 equiv) in a flame-dried flask under argon atmosphere. After the addidition was completed, the mixture was stirred for additional 30 min. A solution of aldehyde (1.0 equiv) in THF (2 M) was then added dropwise over 15 min and the resulting solution. After complete conversion (monitored by TLC), the flask was cooled in an ice-bath and the reaction was quenched by careful addition of a saturated aqueous solution of NH_4Cl. The solution was extracted was extracted with EtOAc (3 times) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by silica gel flash chromatography (petroleum ether/EtOAc gradient).

General procedure C: Benzylic thioethers synthesis: $TsOH.H_2O$ (5 mol%) was added onto a solution of benzylic alcohol (1.0 equiv) and thiol (1.01 equiv) in CH_3CN (0.2 M). Otherwise specifically mentioned, the solution was heated at

reflux over until complete conversion (monitored by TLC). Volatiles were then removed under reduced pressure and the residue was purified by silica gel flash chromatography (petroleum ether/EtOAc gradient).

General procedure D: Quinolin-2-one-based thioethers synthesis: To a solution of amide (1 equiv) in a (2:1) THF:H_2O mixture (0.16 M) were successively added NaOH (4 equiv) and benzyl mercaptan (1.05 eq) at room temperature. The reaction mixture was stirred until completion (monitored by TLC). The solution was then neutralized with HCl [2M] to reach pH = 7 and the THF was removed under reduced pressure. The residue was then diluted in water and the solution was extracted with EtOAc (3 times). The combined organic phases were washed with brine, dried with MgSO4, filtered and concentrated under reduced pressure. The residue was then purified by silica gel flash chromatography (petroleum ether/EtOAc gradient).

General procedure E: N-protection of aniline derivatives: To a solution of aniline (1.0 equiv) in EtOH (c = 1.5 M) was added Boc_2O (1.1 equiv). The resulting solution was stirred for 12 h at room temperature. The solvent was then removed under reduced pressure the residue was purified by silica gel flash chromatography (petroleum ether/EtOAc gradient).

General procedure F: Visible-light photoredox catalytic arylation/amination with tBuOH: In a flame-dried tube (Ø = 10 mm) were placed thioether **3** (0.1 mmol, 1 eq.) and nucleophile **4** (1.5 equiv for **4a**, 3.0 equiv for others). CH_3CN (0.5 mL, 0.2 M), tBuOH (10.0 equiv) and $[Ru(bpy)_3(PF_6)_2]$ (2.2 mg, 2.5 mol %) were successively added and the solution was degassed with O_2 for 40 s. The balloon was left on the top of the tube to maintain the O_2 atmosphere and the solution was stirred under 5 W blue LEDs irradiation at r.t. for 24 h. The solvent

was then removed under reduced pressure and the residue was purified by silica gel flash chromatography (petroleum ether /EtOAc gradient) if not specified.

General procedure G: Visible-light photoredox catalytic arylation/amination without tBuOH: In a flame-dried tube (Ø = 10 mm) were placed thioether **3** (0.1 mmol, 1 equiv) and nucleophile **4** (1.5 equiv for **4a**, 3.0 equiv for others). CH_3CN (0.5 mL, 0.2 M) and $[Ru(bpy)_3(PF_6)_2]$ (2.2 mg, 2.5 mol %) were successively added and the solution was degassed with O_2 for 40 s. The balloon was left on the top of the tube to maintain the O_2 atmosphere and the solution was stirred under 5 W blue LEDs irradiation at r.t. for 24 h. The solvent was then removed under reduced pressure and the residue was purified by silica gel flash chromatography (petroleum ether/EtOAc gradient) if not specified.

Procedure H: Visible-light photoredox catalytic synthesis of **5a** on a preparative scale: In a flame-dried tube (Ø = 15 mm) were placed **3d** (306 mg, 1.0 mmol) and **4a** (252 mg, 1.5 mmol). CH_3CN (5 mL, 0.2 M) and $[Ru(bpy)_3(PF_6)_2]$ (25 mg, 2.5 mol %) were successively added and the solution was degassed with O_2 for 40 s. The balloon was left on the top of the tube to maintain the O_2 atmosphere and the solution was stirred under 5 W blue LEDs irradiation at r.t. for 24 h. The solvent was then removed under reduced pressure and the residue was purified by silica gel flash chromatography (petroleum ether/EtOAc gradient) to afford the desired compound $_{5a}$ as a white solid (327 mg, 94%).

General procedure I: Catalyst-free photo-induced arylation/amination: In a flame-dried tube (Ø = 10 mm) were placed thioether **3** (0.1 mmol, 1 equiv) and nucleophile **4** (1.5 equiv for **4a**, 3.0 equiv for others). CH_3CN (2.5 mL, 0.04 M) was added and the solution was degassed with O_2 for 1 min. The balloon was left on the top of the tube to maintain the O_2 atmosphere and the solution was stirred

under 25 W CFL bulb irradiation at 40 °C for 4 days. 24 h. The solvent was then removed under reduced pressure and the residue was purified by silica gel flash chromatography (petroleum ether/EtOAc gradient) if not specified.

General procedure J: Same procedure than general procedure G but the reaction was performed in a smaller tube (Ø = 6 mm).

4-(hydroxy(phenyl)methyl)phenol: Prepared according to **GP A** from (4-hydroxyphenyl)(phenyl)methanone (2.00 g, 10.0 mmol). White solid (1.82 g, 91% yield). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.18 (s, 1H), 7.42 – 7.36 (m, 2H), 7.32 – 7.25 (m, 2H), 7.23 – 7.14 (m, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 5.73 (d, *J* = 3.9 Hz, 1H), 4.63 (d, *J* = 3.9 Hz, 1H).

2-(hydroxy(phenyl)methyl)phenol: Prepared according to **GP B** from 2-hydroxybenzaldehyde (0.5 mL, 4.7 mmol) and bromobenzene (2.0 mL, 19.0 mmol). White solid (940 mg, 99% yield). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.65 (s, 1H), 7.48 – 7.42 (m, 2H), 7.34 – 7.17 (m, 4H), 7.12 – 7.04 (m, 1H), 6.83 – 6.76 (m, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.13 (d, *J* = 4.1 Hz, 1H), 5.27 (d, *J* = 4.1 Hz, 1H).

(4-methoxyphenyl)(phenyl)methanol: Prepared according to **GP B** from 4-methoxybenzaldehyde (0.58 mL, 4.7 mmol) and bromobenzene (2.0 mL, 19.0 mmol). White solid (967 mg, 96%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.40 (d, *J* = 7.1 Hz, 2H), 7.34 – 7.25 (m, 4H), 7.24 – 7.14 (m, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.77 (d, *J* = 3.9 Hz, 1H), 4.76 – 4.61 (m, 1H), 3.76 (s, 3H).

(4-aminophenyl)(phenyl)methanol: Prepared according to **GP A** from 4-aminobenzophenone (1.0 g, 5.07 mmol). White solid (955 mg, 95%). **^{1}H NMR**

(300 MHz, Acetone-d_6) δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.27 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.21 – 7.13 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 1H), 5.66 (d, *J* = 3.8 Hz, 1H), 4.52 (brs, 1H), 4.46 (d, *J* = 3.8 Hz, 1H).

3-(hydroxy(phenyl)methyl)phenol: Prepared according to **GP B** from 3-hydroxybenzaldehyde (500 mg, 4.1 mmol) and bromobenzene (1.7 mL, 16 mmol). White solid (641 mg, 80%). 1H NMR (300 MHz, Acetone-d6) δ 8.17 (s, 1HOH), 7.53 – 7.36 (m, 2H), 7.33 – 7.25 (m, 2H), 7.24 – 7.16 (m, 1H), 7.11 (dd, J = 7.7, 7.7 Hz, 1H), 6.96 – 6.83 (m, 2H), 6.67 (dd, J = 8.5, 2.5 Hz, 1H), 5.74 (d, J = 3.9 Hz, 1H), 4.74 (d, J = 3.9 Hz, 1HOH).

2-(hydroxy(4-methoxyphenyl)methyl)phenol: Prepared according to **GP B** from salicylaldehyde (1.0 mL, 9.4 mmol) and 4-bromoanisole (4.7 mL, 37.0 mmol). Colourless oil (2.16 g, 99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.36 – 7.14 (m, 4H), 6.95– 6.75 (m, 4H), 5.97 (s, 1H), 3.80 (s, 3H), 2.87 (br s, 1H); **IR (neat)** ν (cm^{-1}): 3339, 2837, 1610, 1586, 1509, 1456, 1241, 1171, 1029, 832, 754; **HRMS** (ESI+, m/z): calculated for $C_{14}H_{13}O_2^+$ 213.0910, found 213.0909.

(4-methoxyphenyl)(m-tolyl)methanol: Prepared according to **GP B** from 3-mehylbenzaldehyde (0.24 mL, 2.0 mmol) and 4-bromoanisole (1.0 mL, 8.0 mmol). Colourless oil (527 mg, 90%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.30 (d, *J* = 8.7 Hz, 2H), 7.25 – 7.11 (m, 3H), 7.07 – 6.96 (m, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.73 (d, *J* = 3.9 Hz, 1H), 4.65 (d, *J* = 3.9 Hz, 1H), 3.75 (s, 3H).

(4-methoxyphenyl)(naphthalen-2-yl)methanol: Prepared according to **GP B** from 2-naphthaldehyde (312 mg, 2.0 mmol) and 4-bromoanisole (1.0 mL, 8.0 mmol). Pale yellow oil (508 mg, 96%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.97

(s, 1H), 7.93 – 7.77 (m, 3H), 7.50 – 7.42 (m, 3H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.95 (d, *J* = 3.8 Hz, 1H), 4.87 (d, *J* = 3.8 Hz, 1H), 3.75 (s, 3H).

(3-fluorophenyl)(4-methoxyphenyl)methanol: Prepared according to **GP B** from 3-fluorobenzaldehyde (210 μL, 2.0 mmol) and 4-bromoanisole (1.0 mL, 8.0 mmol). Colourless oil (531 mg, 97%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.36 – 7.29 (m, 3H), 7.22 – 7.17 (m, 2H), 6.99 – 6.92 (m, 1H), 6.89 – 6.85 (m, 2H), 5.80 (d, J = 3.9 Hz, 1H), 4.88 (d, J = 3.9 Hz, 1HOH), 3.76 (s, 3H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 163.7 (d, *J* = 243.2 Hz), 160.0, 150.0 (d, *J* = 6.8 Hz), 138.1, 130.7 (d, *J* = 8.2 Hz), 128.6, 123.1 (d, *J* = 2.7 Hz), 114.4 , 114.1 (d, *J* = 21.4 Hz), 113.7 (d, *J* = 22.1 Hz), 75.1 (d, *J* = 1.8 Hz), 55.5; **^{19}F NMR** (282 MHz, Acetone-d_6) δ 62.32 .**I**R (neat) ν (cm^{-1}): 3396, 2837, 1614, 1589, 1510, 1447, 1247, 1175, 1032, 834, 793, 761; **HRMS** (ESI^+, m/z): calculated for $C_{14}H_{12}FO^+$ 215.0867, found 215.0877.

(4-methoxyphenyl)(4-(trifluoromethyl)phenyl)methanol: Prepared according to a slightly modified **GP B** from 4-methoxybenzaldehyde (0.79 mL, 6.5 mmol), 4-bromobenzotrifluoride (1.0 mL, 7.2 mmol, 1.1 equiv) and magnesium (176 mg, 7.2 mmol, 1.1 equiv). White solid (987 mg, 54%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.64 (s, 4H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.88 (d, *J* = 3.9 Hz, 1H), 4.99 (d, *J* = 3.9 Hz, 1H), 3.76 (s, 3H).

4-((4-chlorophenyl)(hydroxy)methyl)phenol: Prepared according to **GP A** from 4-chloro-4′-hydroxybenzophenone (1.0 g, 4.3 mmol). White solid (962 mg, 95%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.49 – 7.39 (m, 4H), 7.31 – 7.23 (m, 2H), 7.00 (br s, 1H), 6.90 – 6.81 (m, 2H), 5.82 – 5.76 (m, 1H), 3.85 (d, *J* = 3.6 Hz, 1H).

1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol: To a solution of phenylacetylene (2 mL, 18.2 mmol, 1.2 eq.) in dry THF (12 mL, 1.5 M) at -78 °C was added dropwise *n*-BuLi (11.5 mL, 18.4 mmol, 1.6 M in THF) and the solution was stirred at this temperature for one hour. Then, a solution of 4-methoxybenzaldehyde (1.85 mL, 15.2 mmol) in dry THF (10 mL, 1.5 M) was dropwise added. After complete conversion, a saturated aqueous solution of NH_4Cl was added dropwise to the system. The resulting solution was extracted with AcOEt (3 times). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash chromatography with petroleum ether/AcOEt. White solid (3.39 g, 94%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.6 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.33 (brs, 3H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.65 (d, *J* = 5.7 Hz, 1H), 3.83 (s, 3H), 2.27 (d, *J* = 5.7 Hz, 1H).

6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol: Prepared according to **GP A** from 6-methoxy-1-tetralone (1.0 g, 5.7 mmol). White solid (1.02 g, 99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 4.75 (d, *J* = 4.7 Hz, 1H), 3.79 (s, 3H), 2.87 – 2.62 (m, 2H), 2.14 – 1.84 (m, 3H), 1.85 – 1.72 (m, 1H), 1.67 (br s, 1H).

4-(1-hydroxyethyl)phenol: Prepared according to **GP A** from 4'-hydroxyacetophenone (1.0 g, 7.35 mmol). Yellow solid (550 mg, 55%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.10 (s, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 4.75 (qd, *J* = 6.4, 4.0 Hz, 1H), 3.90 (d, *J* = 4.0 Hz, 1H), 1.36 (d, *J* = 6.4 Hz, 3H).

4-(1-hydroxy-2-methylpropyl)phenol: Prepared according to a modified **GP B**: a commercial solution of isopropylmagnesium chloride (16.0 mL, 32.0 mmol, 2 M in THF) was slowly added on a solution of 4-hydroxybenzaldehyde (1.0 g, 8.2 mmol) in freshly distilled THF (4.0 mL) at 0 °C under argon atmosphere. The solution was then allowed to rise room temperature and stirred complete conversion (monitored by TLC). Work-up and purification were then carried out according to **GP B**. White solid (1.10 g, 91%). Mp: 120 °C; **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.13 - 8.11 (m, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 4.24 (dd, *J* = 6.7, 4.0 Hz, 1H), 3.94 – 3.86 (m, 1H), 1.92 – 1.75 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 157.1, 136.8, 128.5, 115.4, 79.4, 36.4, 19.5, 18.7; **IR (neat)** ν (cm^{-1}): 3349, 2959, 1614, 1515, 1456, 1241, 1007, 827; **HRMS** (ESI+, m/z): calculated for $C_{10}H_{13}O^{+}$ 149.0961, found 149.0957.

4-(1-hydroxyhexyl)phenol: Prepared according to **GP A** from 4-hydroxybenzaldehyde (500 mg, 4.1 mmol) and 1-bromopentane (2.0 mL, 16.0 mmol). White solid (700 mg, 90%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.09 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 4.57 – 4.48 (m, 1H), 3.90 – 3.73 (m, 1H), 1.77 – 1.54 (m, 3H), 1.48 – 1.18 (m, 11H), 0.96 – 0.76 (m, 3H).

1-(2,3,4-trimethoxyphenyl)ethan-1-ol: Prepared according to **GP A** from 2',3',4'-trimethoxyacetophenone (1.0 mL, 5.5 mmol). Colourless oil. (678 mg, 58%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.6 Hz, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 5.05 (q, *J* = 6.5 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 2.44 (brs, 1H), 1.49 (d, *J* = 6.5 Hz, 3H).

4-((ethylthio)(phenyl)methyl)phenol (17a[1]): Prepared according to **GP C** from 4-(hydroxy(phenyl)methyl)phenol (200 mg, 1.0 mmol) and ethanethiol (73 μL,

1.01 mmol). Colourless oil (164 mg, 67%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.33 – 7.18 (m, 6H), 6.77 (d, *J* = 8.6 Hz, 2H), 5.13 (s, 1H), 2.39 (q, *J* = 7.3 Hz, 2H), 1.21 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.7, 141.8, 133.7, 129.5, 128.5, 128.2, 127.0, 115.3, 53.1, 26.2, 14.2; **IR (neat)** ν (cm^{-1}): 3335, 3025, 2967, 2926, 1611, 1597, 1509, 1449, 1227, 1171, 698; **HRMS** (ESI+, m/z): calculated for $C_{13}H_{11}O^+$ 183.0804, found 183.0806.

4-((tert-butylthio)(phenyl)methyl)phenol (17a[2]): Prepared according to **GP C** from 4-(hydroxy(phenyl)methyl)phenol (200 g, 1.0 mmol) and 2-methylpropane-2-thiol (1.01 mmol, 0.12 mL). White solid (233 mg, 86%). Mp: 113 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.32 – 7.25 (m, 4H), 7.21 – 7.15 (m, 1H), 6.77 – 6.72 (m, 2H), 5.17 (s, 1H), 1.25 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.3, 143.4, 135.5, 129.6, 128.4, 128.3, 126.7, 115.2, 51.5, 44.6, 31.3; **IR (neat)** ν (cm^{-1}): 3376, 2960, 1612, 1597, 1509, 1451, 1364, 1238, 1160, 801, 697; **HRMS** (ESI+, m/z): calculated for $C_{13}H_{11}O^+$ 183.0804, found 183.0809.

4-(phenyl(phenylthio)methyl)phenol (17a[3]): Prepared according to **GP C** from 4-(hydroxy(phenyl)methyl)phenol (200 g, 1.0 mmol) and thiophenol (1.01 mmol, 0.10 mL). White solid (249 mg, 85%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 – 7.38 (m, 2H), 7.34 – 7.08 (m, 10H), 6.75 (d, *J* = 8.6 Hz, 1H), 5.50 (s, 1H).

4-((benzylthio)(phenyl)methyl)phenol (17a): Prepared according to **GP C** from 4-(hydroxy(phenyl)methyl)phenol (1.0 g, 5.0 mmol) and benzyl mercaptan (0.59 mL, 5.05 mmol). White solid (1.10 g, 72%); Mp: 78 °C. **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.33 (s, 1H), 7.45 – 7.39 (m, 2H), 7.35 – 7.22 (m, 10H), 6.80 (d, *J* = 8.6 Hz, 2H), 5.04 (s, 1H), 3.57 (s, 2H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 157.4 , 142.9 , 139.2 , 133.0 , 130.3 , 129.8 , 129.3 , 129.2 , 129.1 , 127.8 ,

127.7, 116.1 , 53.7 , 37.1; **IR (neat)** ν (cm-1): 3366, 3026, 1610, 1597, 1509, 1492, 1452, 1238, 1171, 697; **HRMS** (ESI+, m/z): calculated for $C_{13}H_{11}O^+$ 183.0804, found 183.0806.

2-((benzylthio)(phenyl)methyl)phenol (17b): Prepared according to **GP C** from 2-(hydroxy(phenyl)methyl)phenol (500 mg, 2.5 mmol) and benzyl mercaptan (0.30 mL, 2.53 mmol). White solid (402 mg, 88%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 – 7.14 (m, 11H), 7.08 – 6.72 (m, 4H), 5.11 (s, 1H), 3.63 (s, 2H).

3-((benzylthio)(phenyl)methyl)phenol (17c): Prepared according to **GP C** from 3-(hydroxy(phenyl)methyl)phenol (300 mg, 1.5 mmol) and benzyl mercaptan (0.18 mL, 1.52 mmol). Colourless oil (390 mg, 85%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.28 (s, 1H), 7.45 – 7.41 (m, 2H), 7.36 – 7.21 (m, 8H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.72 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1H), 5.04 (s, 1H), 3.60 (s, 2H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 158.5, 143.9, 142.5, 139.1, 130.4, 129.8, 129.3, 129.24, 129.20, 128.0, 127.8, 120.4, 116.1, 115.0, 54.2, 37.2 ; **IR (neat)** ν (cm^{-1}): 3377, 3027, 1597, 1493, 1452, 1240, 734, 700; **HRMS** (ESI+, m/z): calculated for $C_{13}H_{11}O^+$ 183.0804, found 183.0805.

benzyl((4-methoxyphenyl)(phenyl)methyl)sulfane (17d): Prepared according to **GP C** from (4-methoxyphenyl)(phenyl)methanol (500 mg, 2.33 mmol) and benzyl mercaptan (0.33 mL, 2.35 mmol). White solid (723 mg, 96%). Mp: 66.5 °C. **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.47 – 7.38 (m, 2H), 7.38 – 7.18 (m, 9H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.07 (s, 1H), 3.77 (s, 3H), 3.58 (s, 2H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 159.8, 142.8, 139.2, 134.2, 130.3, 129.8, 129.3, 129.2, 129.1, 127.9, 127.7, 114.7, 55.5, 53.6, 37.1; **IR (neat)** ν (cm-1): 3060, 3027,

2834, 1608, 1500, 1493, 1452, 1302, 1248, 1175, 1032, 697; **HRMS** (ESI+, m/z): calculated for $C_{14}H_{13}O^+$ 197.0961, found 197.0967.

tert-butyl (4-((benzylthio)(phenyl)methyl)phenyl)carbamate (17e): Prepared according to **GP E** from 4-((benzylthio)(phenyl)methyl)aniline (200 mg, 0.65 mmol). Clear oil (250 mg, 94%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.39 (brs, 1H), 7.55 – 7.51 (m, 2H), 7.44 – 7.40 (m, 2H), 7.36 – 7.23 (m, 10H), 5.07 (s, 1H), 3.59 (s, 2H), 1.47 (s, 9H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 160.5, 153.7, 142.7, 139.7, 139.2, 136.0, 129.8, 129.6, 129.4, 129.24, 129.16, 127.9, 127.7, 80.0, 53.8, 37.2, 28.5; **IR (neat)** ν (cm^{-1}): 3333, 3027, 2978, 1727, 1701, 1595, 1519, 1410, 1316, 1158, 1053, 698; **HRMS** (ESI+, m/z): $[M+Na]^+$ calculated for $C_{25}H_{27}NNaO_2S^+$ 428.1655, found 428.1664. **4-((benzylthio)(phenyl)methyl)aniline**: Prepared according to **GP C** from (4-aminophenyl)(phenyl)methanol (500 mg, 2.5 mmol) and benzyl mercaptan (0.30 mL, 2.53 mmol). Yellow pale solid (622 mg, 81%). Mp: 77 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 12H), 6.64 (d, J = 8.4 Hz, 2H), 4.90 (s, 1H), 3.57 (s, 2H), 3.57 (brs, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.4, 141.6, 138.2, 130.9, 129.4, 129.0, 128.42, 128.37, 128.3, 126.9, 126.8, 115.1, 52.8, 36.6; **IR (neat)** ν (cm-1): 3450, 3370, 3222, 3058, 3026, 2916, 1621, 1512, 1492, 1452, 1282, 1178, 1072, 1029, 738, 697; **HRMS** (ESI+, m/z): calculated for $C_{22}H_{23}N_2S^+$ 347.1576, found 347.1576.

benzhydryl(benzyl)sulfane (17f): Prepared according to **GP C** from commercial diphenylmethanol (921 mg, 5.0 mmol) and benzyl mercaptan (0.59 mL, 5.05 mmol). White solid (1.41 g, 97%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 4H), 7.40 – 7.23 (m, 11H), 5.00 (s, 1H), 3.61 (s, 2H).

benzyl(bis(4-methoxyphenyl)methyl)sulfane (17h): Prepared according to **GP C** from commercial bis(4-methoxyphenyl)methanol (500 mg, 2.05 mmol) and benzyl mercaptan (0.24 mL, 2.07 mmol). White solid (657 mg, 97%). Mp: 77 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 9H), 6.86 – 6.81 (m, 4H), 4.88 (s, 1H), 3.78 (s, 6H), 3.53 (s, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.6, 158.6, 133.4, 129.4, 129.0, 128.4, 126.9, 113.9, 55.3, 51.9, 36.6; **IR (neat)** ν (cm^{-1}): 3001, 2953, 2834, 1607, 1582, 1498, 1454, 1301, 1247, 1174, 1033, 815, 702; **HRMS** (ESI+, m/z): calculated for $C_{15}H_{15}O_2^+$ 227.1067, found 227.1091.

2-((benzylthio)(4-methoxyphenyl)methyl)phenol (17g): Prepared according to **GP C** from 2-(hydroxy(4-methoxyphenyl)methyl)phenol (700 mg, 3.0 mmol) and benzyl mercaptan (0.36 mL, 3.03 mmol). Colourless oil (879 mg, 86%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 7H), 6.98 – 6.84 (m, 6H), 5.08 (s, 1H), 3.80 (s, 3H), 3.62 (d, J = 1.9 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.9, 155.0, 137.2, 130.5, 130.2, 129.8, 129.1, 128.9, 128.6, 127.3, 124.9, 120.6, 117.5, 114.0, 55.2, 49.1, 36.4; **IR (neat)** ν (cm-1): 3399, 3029, 2835, 1608, 1508, 1454, 1248, 1177, 1032, 754; **HRMS** (ESI+, m/z): calculated for $C_{14}H_{13}O_2^+$ 213.0910, found 213.0919.

benzyl((4-methoxyphenyl)(m-tolyl)methyl)sulfane (17i): Prepared according to **GP C** from (4-methoxyphenyl)(m-tolyl)methanol (300 mg, 1.3 mmol) and benzyl mercaptan (0.15 mL, 1.31 mmol). White solid (366 mg, 84%). Mp: 34 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 9H), 7.14 – 7.10 (m, 1H), 6.96 – 6.92 (m, 2H), 4.97 (s, 1H), 3.87 (s, 3H), 3.64 (s, 2H), 2.41 (s, 3H). **13C NMR** (75 MHz, $CDCl_3$) δ 159.6, 158.6, 141.2, 138.1, 133.2, 129.5, 129.0 (3C), 128.4 (3C), 127.9, 126.9, 125.4, 113.9, 55.2, 52.6, 36.6, 21.4. **IR (neat)** ν (cm^{-1}): 3028, 1606, 1508, 1453, 1248, 1175, 1033, 832, 758, 697; **HRMS** (ESI+, m/z): calculated for $C_{15}H_{15}O^+$ 211.1117, found 211.1114.

benzyl((4-methoxyphenyl)(naphthalen-2-yl)methyl)sulfane (17j): Prepared according to **GP C** from (4-methoxyphenyl)(naphthalen-2-yl)methanol (200 mg, 0.76 mmol) and benzyl mercaptan (90 µL, 0.77 mmol). Colourless oil (263 mg, 93%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.92 – 7.85 (m, 4H), 7.59 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.35 – 7.21 (m, 5H), 6,91 (d, *J* = 8.6 Hz, 2H), 5.26 (s, 1H), 3.78 (s, 3H), 3.64 (s, 2H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 160.5, 140.2, 139.2, 134.1, 133.6, 130.4, 129.8 (3C), 129.2, 129.1, 128.7, 128.4, 127.8, 127.6, 127.5, 127.1, 126.8, 114.8, 55.5, 53.8, 37.2; **IR (neat)** ν (cm^{-1}): 3000, 1607, 1508, 1453, 1248, 1176, 1033, 816, 759, 701; **HRMS** (ESI+, m/z): calculated for $C_{18}H_{15}O^{+}$ 247.1117, found 247.1124.

benzyl((3-fluorophenyl)(4-methoxyphenyl)methyl)sulfane (17k): Prepared according to **GP C** from (3-fluorophenyl)(4-methoxyphenyl)methanol (300 mg, 1.3 mmol) and benzyl mercaptan (0.15 mL, 1.31 mmol). White solid (358 mg, 81%). Mp: 84 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 8H), 7.13 – 7.08 (m, 2H), 6.94 – 6.82 (m, 3H), 4.87 (s, 1H), 3.78 (s, 3H), 3.55 (s, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.9 (d, *J* = 245.9 Hz), 158.8, 144.0 (d, *J* = 6.9 Hz), 137.8, 132.4, 129.9 (d, *J* = 8.3 Hz), 129.5, 129.0 , 128.4, 127.0, 124.1 (d, *J* = 2.8 Hz), 115.3 (d, *J* = 22.1 Hz), 114.0 (d, *J* = 21.2 Hz), 114.0, 55.3, 52.0 (d, *J* = 1.7 Hz), 36.6; **^{19}F NMR** (282 MHz, $CDCl_3$) δ –112.83; **IR (neat)** ν (cm^{-1}): 2838, 1610, 1587, 1509, 1486, 1251, 1176, 1034, 764, 702; **HRMS** (ESI+, m/z): calculated for $C_{14}H_{12}FO^{+}$ 215.0867, found 215.0869.

benzyl((4-methoxyphenyl)(4-(trifluoromethyl)phenyl)methyl)sulfane (17l): Prepared according to **GP C** from (4-methoxyphenyl)(4-(trifluoromethyl)phenyl)methanol (300 mg, 1.0 mmol) and benzyl mercaptan (0.12 mL, 1.01 mmol). White solid (373 mg, 90%). Mp: 46 °C. **^{1}H NMR** (300

MHz, $CDCl_3$) δ 7.55 – 7.44 (m, 4H), 7.29 – 7.17 (m, 7H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.91 (s, 1H), 3.76 (s, 3H), 3.54 (s, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.0, 145.6, 137.7, 132.1, 129.5, 129.0, 128.8, 128.5, 127.1, 125.5, 124.1 (q, *J* = 272.9 Hz), 114.1, 55.3, 52.2, 36.7; **^{19}F NMR** (282 MHz, $CDCl_3$) δ –62.49; **IR (neat)** ν (cm^{-1}): 3030, 2837, 1610, 1509, 1324, 1250, 1164, 1122, 1067, 1017, 817, 701; **HRMS** (ESI+, m/z): calculated for $C_{15}H_{12}F_3O^+$ 265.0835, found 265.0841.

4-((benzylthio)(4-chlorophenyl)methyl)phenol (17m): Prepared according to **GP C** from 3-(hydroxy(phenyl)methyl)phenol (500 mg, 2.13 mmol) and benzyl mercaptan (0.25 mL, 2.15 mmol). Yellow solid (618 mg, 85%). Mp: 76 °C. **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.35 (s, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.38 – 7.20 (m, 9H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.05 (s, 1H), 3.60 (s, 2H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 157.6, 141.9, 139.0, 133.0, 132.5, 130.9, 130.3, 129.8, 129.3, 129.2, 127.8, 116.3, 53.0, 37.2; **IR (neat)** ν (cm^{-1}): 3369, 3026, 1610, 1509, 1488, 1171, 1089, 1014, 822, 700; **HRMS** (ESI+, m/z): calculated for $C_{13}H_{10}ClO^+$ 217.0415, found 217.0412.

3-((benzylthio)(phenyl)methyl)-1H-indole (17n): Prepared according to **GP C** from (1H-indol-3-yl)(phenyl)methanol (250 mg, 1.1 mmol) and benzyl mercaptan (0.13 mL, 1.11 mmol). Yellow oil. (238 mg, 65%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.45-7.32 (m, 3H), 7.25-7.12 (m, 9H), 7.05 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 6.95 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H,), 6.87 (d, *J* = 2.5 Hz, 1H), 5.12 (s, 1H), 3.57 – 3.43 (m, 2H).

2-((benzylthio)diphenylmethyl)-1H-indole (17o): Prepared according to **GP C** from (1H-indol-2-yl)diphenylmethanol (150 mg, 0.5 mmol) and benzyl mercaptan (60 µL, 0.51 mmol). Yellow oil. (64 mg, 32%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.50-7.35 (m, 5H), 7.30-6.95 (m, 14H), 6.26 (s, 1H), 3.41

(s, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.8, 140.4, 137.3, 136.5, 130.2, 129.1, 128.72, 128.67, 128.4, 127.4, 127.3, 122.5, 120.8, 120.1, 111.0, 106.1, 63.3, 37.0; **IR (neat)** ν (cm^{-1}): 3407, 3058, 2850, 1598, 1490, 1454, 1445, 1405, 1289, 1183, 1130, 1032, 798, 779, 735; **HRMS** (ESI+, m/z): [M+H]+ calculated for $C_{28}H_{24}NS^+$ 406.1624, found 406.1609.

3-((benzylthio)(4-hydroxyphenyl)methyl)quinolin-2(1H)-one (17p): Prepared according to **GP D** from (E)-4-(3-((2-formylphenyl)amino)-3-oxoprop-1-en-1-yl)phenyl acetate (800 mg, 2.55 mmol). Pale solid. (275 mg, 23%). **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.39 (s, 1H), 8.18 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.47 (dd, J = 7.5 Hz, 1H), 7.35 – 7.10 (m, 9H), 6.69 (d, *J* = 8.0 Hz, 2H), 5.28 (s, 1H), 3.63 (s, 2H).

3-((benzylthio)(4-hydroxyphenyl)methyl)-6-fluoroquinolin-2(1H)-one (17q): Prepared according to **GP D** from (E)-4-(3-((4-fluoro-2-formylphenyl)amino)-3-oxoprop-1-en-1-yl)phenyl acetate (200 mg, 0.61 mmol).White solid. (95 mg, 46%). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.88 (s, 1H), 9.39 (s, 1H), 8.18 (s, 1H), 7.66 (d, *J* = 9.1 Hz, 1H), 7.47 – 7.05 (m, 9H), 6.68 (d, *J* = 8.1 Hz, 2H), 5.27 (s, 1H), 3.63 (s, 2H).

3-((benzylthio)(4-hydroxyphenyl)methyl)-7-chloroquinolin-2(1H)-one (17r): Prepared according to **GP D** from (E)-4-(3-((5-chloro-2-formylphenyl)amino)-3-oxoprop-1-en-1-yl)phenyl acetate (260 mg, 0.76 mmol).White solid. (205 mg, 66%). **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.90 (s, 1H), 9.39 (s, 1H), 8.19 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.19 (m, 7H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 5.23 (s, 1H), 3.63 (s, 2H).

benzyl(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)sulfane (17s): Prepared according to **GP C** from 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (500 mg, 2.1 mmol) and benzyl mercaptan (0.25 mL, 2.12 mmol). White solid (602 mg, 83%). Mp: 58 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.46 – 7.16 (m, 8H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.71 (s, 1H), 3.99 (d, *J* = 13.4 Hz, 1H), 3.75 (d, *J* = 13.4 Hz, 1H), 3.74 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.2 , 137.8 , 131.8 , 129.8, 129.2, 129.0, 128.5, 128.3 (3C), 127.1, 123.0, 114.0, 87.4, 86.0, 55.3, 38.4, 36.6; **IR (neat)** ν (cm^{-1}): 3061, 3029, 2931, 2835, 1608, 1509, 1490, 1251, 1173, 1032, 833, 756, 691; **HRMS** (ESI+, m/z): [M+H]+ calculated for $C_{23}H_{21}OS^{+}$ 345.1308, found 345.1322.

benzyl(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)sulfane (17t): Prepared according to **GP C** from 6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (1.0 g, 5.6 mmol) and benzyl mercaptan (0.66 mL, 5.7 mmol). Clear oil (1.36 g, 85%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.18 (m, 6H), 6.73 – 6.69 (m, 1H), 6.60 (s, 1H), 3.99 – 3.98 (m, 1H), 3.85 – 3.73 (m, 5H), 2.85 – 2.67 (m, 2H), 2.26 – 1.95 (m, 3H), 1.81 – 1.75 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.2, 138.8 , 138.7, 131.4, 128.9, 128.5 (3C), 126.9, 113.3, 112.2, 55.2, 42.8, 36.1, 29.5, 29.0, 19.0; **IR (neat)** ν (cm^{-1}): 3025, 2932, 2834, 1606, 1498, 1452, 1272, 1252, 1234, 1037, 702; **HRMS** (ESI+, m/z): calculated for $C_{11}H_{13}O^{+}$ 161.0961, found 161.0963.

ethyl(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)sulfane (17t^{1}): Prepared according to **GP C** from 6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (500 mg, 2.8 mmol) and ethanethiol (0.20 mL, 2.83 mmol). Clear oil (184 mg, 30%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 4.09 (t, *J* = 4.3 Hz, 1H), 3.77 (s, 2H), 2.86 – 2.46 (m, 4H), 2.23 – 1.91 (m, 3H), 1.82 – 1.64 (m, 1H), 1.29 (t, *J* = 7.4 Hz, 2H); **^{13}C**

NMR (75 MHz, $CDCl_3$) δ 158.3, 138.8, 131.4, 129.1, 113.6, 112.3, 55.3, 43.2, 29.6, 29.4, 25.6, 19.1, 14.9. **IR (neat)** ν (cm^{-1}): 2929, 2834, 1607; 1499, 1452, 1328, 1234, 1191, 1161, 1120, 1038, 938, 871, 835, 818, 737, 715, 682; **HRMS** (ESI+, m/z): calculated for $C_{11}H_{13}O^+$ 161.0961, found 161.0955.

4-(1-(benzylthio)ethyl)phenol (17u): Prepared according to **GP C** from 4-(1-hydroxyethyl)phenol (300 mg, 2.2 mmol) and benzyl mercaptan (0.26 mL, 2.22 mmol). Yellow solid (488 mg, 86%). Mp: 68 °C. **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.29 (s, 1H), 7.32 – 7.16 (m, 7H), 6.83 – 6.78 (m, 2H), 3.82 (q, *J* = 7.0 Hz, 1H), 3.64 – 3.43 (m, 2H), 1.47 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 157.3, 139.8, 135.5, 129.7, 129.3, 129.2, 127.5, 116.0, 43.8, 36.2, 23.0; **IR (neat)** ν (cm^{-1}): 3351, 2965, 1611, 1511, 1452, 1494, 1372, 1219, 1171, 833, 704; **HRMS** (ESI+, m/z): calculated for $C_8H_9O^+$ 121.0648, found 121.0648.

4-(1-(benzylthio)-2-methylpropyl)phenol (17v): Prepared according to **GP C** from 4-(1-hydroxy-2-methylpropyl)phenol (500 mg, 3.0 mmol) and benzyl mercaptan (0.36 mL, 3.03 mmol). White solid (325 mg, 40%). Mp: 63 °C. **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.24 (s, 1H), 7.32 - 7.03 (m, 2H), 6.85 – 6.80 (m, 1H), 3.49 – 3.34 (m, 3H), 1.95 (dq, *J* = 7.9, 6.7 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 157.2, 139.8, 133.2, 130.7, 129.8, 129.1, 127.5, 115.8, 57.4, 36.0, 34.8, 21.5, 21.1; **IR (neat)** ν (cm^{-1}): 3351, 2959, 1610, 1509, 1453, 1366, 1238, 1170, 1106, 850, 702; **HRMS** (ESI+, m/z): calculated for $C_{10}H_{13}O^+$ 149.0961, found 149.0962.

4-(1-(benzylthio)hexyl)phenol (17w): Prepared according to **GP C** from 4-(1-hydroxyhexyl)phenol (300 mg, 1.5 mmol) and benzyl mercaptan (0.13 mL, 1.52 mmol). Colourless oil (399 mg, 88%). **^{1}H NM**R (300 MHz, Acetone-d_6) δ 8.24 (s, 1H), 7.32 – 7.19 (m, 5H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H),

3.64 (dd, *J* = 8.6, 6.4 Hz, 1H), 3.56 – 3.42 (m, 2H), 1.87 – 1.67 (m, 2H), 1.31 – 1.13 (m, 6H), 0.83 – 0.79 (m, 3H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 160.5, 157.3, 134.4, 129.9, 129.8, 129.1, 127.5, 116.0, 49.4, 37.3, 35.9, 32.2, 28.0, 23.1, 14.2; **IR (neat)** ν (cm^{-1}): 3347, 2929, 2857, 1611, 1511, 1453, 1234, 1170, 834, 701; **HRMS** (ESI+, m/z): calculated for $C_{12}H_{17}O^+$ 177.1274, found 177.1274.

benzyl(1-(2,3,4-trimethoxyphenyl)ethyl)sulfane (17x): Prepared according to **GP C** from 1-(2,3,4-trimethoxyphenyl)ethan-1-ol (670 mg, 3.16 mmol) and benzyl mercaptan (0.37 mL, 3.20 mmol). Clear oil (715 mg, 71%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.32 – 7.24 (m, 4H), 7.26 – 7.18 (m, 1H), 7.13 (d, J = 8.7 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 4.27 (q, J = 7.1 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.65 (s, 2H), 1.48 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 153.7 (2C), 152.2, 139.8, 130.3, 129.7, 129.1, 127.5, 122.7, 108.9, 61.4, 60.7, 56.3, 37.1, 36.5, 22.5; **IR (neat)** ν (cm^{-1}): 2934, 1598, 1493, 1464, 1416, 1288, 1097, 1024, 698; **HRMS** (ESI+, m/z): calculated for $C_{11}H_{15}O_3^+$ 195.1016, found 195.1014.

methyl 2-(benzhydrylthio)benzoate (17y): Prepared according to **GP C** from commercial diphenylmethanol (461 mg, 2.5 mmol) and methyl 2-mercaptobenzoate (0.35 mL, 2.53 mmol). White solid (762 mg, 91%). Mp: 99 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.50 – 7.45 (m, 4H), 7.38 – 7.02 (m, 9H), 5.69 (s, 1H), 3.93 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.1, 141.5, 140.5, 132.3, 131.2, 128.82, 128.78, 127.9, 127.49, 127.47, 124.3, 55.4, 52.3; **IR (neat)** ν (cm^{-1}): 2955, 1711, 1585, 1490, 1465, 1433, 1289, 1277, 1253, 1186, 1147, 1110, 1067, 1047, 964, 910, 822, 731, 693. **HRMS** (ESI+, m/z): calculated for $C_{21}H_{19}O_2S^+$ 335.1100, found 335.1103.

2-(benzhydrylthio)pyridine (17z): Prepared according to **GP C** from commercial diphenylmethanol (461 mg, 2.5 mmol) and pyridine-2-thiol (281 mg,

2.53 mmol). Yellow solid (648 mg, 93%). Mp: 75 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.35 (ddd, *J* = 5.0, 1.9, 1.0 Hz, 1H), 7.48 – 7.41 (m, 4H), 7.38 (ddd, *J* = 8.0, 7.5, 1.9 Hz, 1H), 7.31 – 7.14 (m, 6H), 7.08 (dt, *J* = 8.0, 1.0 Hz, 1H), 6.90 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 6.31 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5, 149.6, 141.5, 136.2, 128.7, 128.6, 127.2, 122.4, 119.9, 52.8; **IR (neat)** ν (cm^{-1}): 3068, 3044, 3027, 1577, 1556, 1490, 1449, 1412, 1285, 1122, 1077, 1043, 984, 834, 745; **HRMS** (ESI+, m/z): calculated for $C_{18}H_{16}NS^+$ 278.0998, found 278.1001.

tert-butyl 3,5-dimethoxyphenylcarbamate: Prepared according to **GP E** from 3,5-dimethoxyaniline (500 mg, 3.26 mmol). White solid (634 mg, 77%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.59 (d, *J* = 2.2 Hz, 2H), 6.45 (br s, 1H), 6.16 (t, *J* = 2.2 Hz, 1H), 3.77 (s, 6H), 1.51 (s, 6H).

di-tert-butyl 1,3-phenylenedicarbamate: Prepared according to **GP E** from 1,3-benzenediamine (500 mg, 4.62 mmol). White solid (1.3 g, 90%). Mp: 148 °C. **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.36 (br s, 2H), 7.77 (s, 1H), 7.26 – 7.01 (m, 3H), 1.47 (s, 18H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 153.7, 141.0, 129.6, 113.2, 109.2, 79.8, 28.5; **IR (neat)** ν (cm^{-1}): 3325, 2979, 1698, 1611, 1532, 1491, 1421, 1367, 1241, 1156, 1054, 773; **HRMS** (ESI+, m/z): calculated for $C_{16}H_{24}N_2NaO_4^+$ 331.1628, found 331.1637.

tert-butyl (3-methoxyphenyl)carbamate: Prepared according to **GP E** from 3-methoxyaniline (500 µL, 4.4 mmol). White solid (949 mg, 96%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.10 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.64 – 6.55 (m, 1H), 6.52 (br s, 1H), 3.79 (s, 3H), 1.52 (s, 9H).

4-(phenyl(2,4,6-trimethoxyphenyl)methyl)phenol (18a): Prepared from 4-((benzylthio)(phenyl)methyl)phenol **17a** and **TMB**. White solid. Mp: 149 °C. **GP F**: (34.6 mg, 99%). **GP G**: (32.9 mg, 94%). **GP I**: (30.1 mg, 86%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 – 7.12 (m, 5H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 2H), 6.16 (s, 2H), 5.99 (s, 1H), 4.74 (br s, 1H), 3.81 (s, 3H), 3.59 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.9, 159.1, 153.3, 144.5, 136.2, 130.3, 128.9, 127.5, 125.2, 114.4, 113.9, 91.7, 55.7, 55.2, 44.3; **IR (neat)** ν (cm^{-1}): 3409, 2938, 2837, 16002, 1510, 1454, 1223, 1204, 1145, 1115, 812, 699; **HRMS** (ESI+, m/z): calculated for $C_{22}H_{23}O_4^+$ 351.1595, found 351.1585.

2-(phenyl(2,4,6-trimethoxyphenyl)methyl)phenol (18b): Prepared from 2-((benzylthio)(phenyl)methyl)phenol and **TMB**. White solid. Mp: 119 °C. **GP F**: (33.6 mg, 96%). **GP G**: (31.9 mg, 94%). **^{1}H NMR** (500 MHz, Acetone-d_6) δ 7.77 (s, 1H), 7.16 (dd, *J* = 7.5 Hz, 2H), 7.09 – 6.99 (m, 5H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.72 (dd, *J* = 7.5 Hz, 1H), 6.27 (s, 1H), 6.26 (s, 2H), 3.80 (s, 3H), 3.57 (s, 6H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 161.3, 160.2, 156.1, 145.4, 132.1, 130.1, 129.2, 128.0, 127.7, 125.6, 119.7, 115.7, 113.9, 92.8, 56.1, 55.5, 40.5; **IR (neat)** ν (cm^{-1}): 3393, 2938, 1589, 1492, 1454, 1417, 1223, 1203, 1147, 1113; **HRMS** (ESI+, m/z): [M+H]+ calculated for $C_{22}H_{23}O_4^+$ 351.1591, found 351.1587.

3-(phenyl(2,4,6-trimethoxyphenyl)methyl)phenol (18c): Prepared from 3-((benzylthio)(phenyl)methyl)phenol **3f** and **4a**. Colourless oil. **GP F**: (traces, 1%). **GP I**: (3.5 mg, 10%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.02 (m, 6H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.67 – 6.60 (m, 2H), 6.15 (s, 1H), 5.99 (s, 2H), 4.54 (br s, 1H), 3.80 (s, 3H), 3.59 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.1, 159.3, 155.3, 146.2, 144.1, 129.3, 128.8, 127.7, 125.6, 121.7, 116.3, 113.8, 112.5, 92.0, 55.9, 55.4, 41.3; **HRMS** (ESI+, m/z) calculated for $C_{22}H_{23}O_4^+$ 351.1591, found 351.1591.

1,3,5-trimethoxy-2-((4-methoxyphenyl)(phenyl)methyl)benzene (18d): Prepared from **17d** and **TMB**. White solid. Mp: 110 °C. **GP F**: (23.5 mg, 64%). **GP G**: (30.9 mg, 85%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.23 – 7.08 (m, 7H), 6.79 (d, *J* = 8.8 Hz, 2H,), 6.26 (s, 2H), 5.98 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.61 (s, 6H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 161.3, 159.9, 158.6, 145.7, 136.8, 131.0, 129.7, 128.2, 126.0, 114.3, 113.8, 92.6, 56.0, 55.6, 55.4, 45.3; **IR (neat)** ν (cm^{-1}): 2999, 2936, 2836, 1603, 1509, 1463, 1204, 1146, 1116, 1036; HRMS (ESI+, m/z): [M+H]+ calculated for $C_{23}H_{25}O_4^+$ 365.1747, found 365.1756.

tert-butyl (4-(phenyl(2,4,6-trimethoxyphenyl)methyl)phenyl)carbamate (18e): Prepared from tert-butyl (4-((benzylthio)(phenyl)methyl)phenyl) carbamate and **TMB**. Pale yellow solid. Mp: 60 °C. **GP F**: (44.1 mg, 98%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 – 7.09 (m, 9H), 6.42 (s, 1H), 6.14 (s, 2H), 6.00 (s, 1H), 3.80 (s, 3H), 3.59 (s, 6H), 1.51 (s, 9H). 13C NMR (75 MHz, Acetone-d_6) δ 161.3, 160.0, 153.8, 145.5, 138.8, 138.1, 130.2, 129.7, 128.3, 126.0, 118.4, 114.1, 92.5, 79.7, 56.0, 55.5, 45.4, 28.6; **IR (neat)** ν (cm^{-1}): 3339, 2937, 1725, 1592, 1519, 1410, 1224, 1161, 1116, 1054, 951, 814, 699; HRMS (ESI+, m/z): [M+Na]+ calculated for $C_{27}H_{31}NNaO_5^+$ 472.2094, found 472.2112.

((2,4,6-trimethoxyphenyl)methylene)dibenzene (18f): Prepared from benzhydryl(benzyl)sulfane **17f** and **TMB**. Pale yellow solid. Mp: 123 °C. **GP F**: (5.0 mg, 15%). **GP G**: (4.0 mg, 94%). **GP I**: (13.0 mg, 39%). **GP J**: (14.3 mg, 43%). **^{1}H NMR** (300 MHz, CDCl3) δ 7.29 – 7.09 (m, 10H), 6.15 (s, 2H), 6.05 (s, 1H), 3.80 (s, 3H), 3.58 (s, 6H).

2-((4-methoxyphenyl)(2,4,6-trimethoxyphenyl)methyl)phenol (18g): Prepared from 2-((benzylthio)(4-methoxyphenyl)methyl)phenol and **TMB**. Pale yellow solid. Mp: 86 °C. **GP F**: (27.7 mg, 73%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.63 (s, 1H), 7.09 – 6.94 (m, 4H), 6.80 – 6.69 (m, 4H), 6.26 (s, 2H), 6.20 (s, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.59 (s, 6H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 161.2, 160.2, 158.3, 156.0, 136.9, 132.1, 130.7, 130.2, 127.5, 119.6, 115.7, 113.9, 113.5, 92.8, 56.1, 55.5, 55.4, 39.8; **IR (neat)** ν (cm^{-1}): 3409, 2938, 2837, 1606, 1588, 1509, 1455, 1203, 1113, 1035, 756; **HRMS** (ESI+, m/z) calculated for $C_{23}H_{25}O_5^+$ 381.1697, found 381.1682.

4,4'-((2,4,6-trimethoxyphenyl)methylene)bis(methoxybenzene) (18h): Prepared from benzyl(bis(4-methoxyphenyl)methyl)sulfane and **TMB**. Pink solid. **GP F**: (41.4 mg, 98%). **GP G**: (33.5 mg, 85%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.07 (dd, *J* = 8.9, 0.8 Hz, 4H), 6.77 (d, *J* = 8.8 Hz, 4H), 6.25 (s, 2H), 5.92 (s, 1H), 3.79 (s, 3H), 3.74 (s, 6H), 3.62 (s, 6H).

1,3,5-trimethoxy-2-((4-methoxyphenyl)(m-tolyl)methyl)benzene (18i): Prepared from benzyl((4-methoxyphenyl)(m-tolyl)methyl)sulfane and **TMB**. Colourless oil. **GP F**: (32.1 mg, 85%). **GP G**: (32.9 mg, 87%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 7.3 Hz, 1H), 7.02 – 6.93 (m, 3H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.16 (s, 2H), 5.98 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.60 (s, 6H), 2.28 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.1, 159.4, 157.6, 144.7, 137.1, 136.5, 130.4, 129.9, 127.6, 126.3, 126. 2, 114.2, 113.2, 92.0, 56.0, 55.5, 55.4, 44.5, 21.8; **IR (neat)** ν (cm^{-1}): 2999, 2935, 2836,1605, 1590, 1509, 1463, 1221, 1203, 1115, 1037, 812; **HRMS** (ESI+, m/z): calculated for $C_{24}H_{27}O_4^+$ 379.1904, found 379.1916.

2-((4-methoxyphenyl)(2,4,6-trimethoxyphenyl)methyl)naphthalene (18j): Prepared from **17j** and **TMB**. Red solid. Mp: 80 °C. **GP F**: (27.3 mg, 66%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.83 – 7.80 (m, 1H), 7.74 – 7.20 (m, 2H), 7.57 (s, 1H), 7.41 – 7.32 (m, 3H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.28 (s, 2H), 6.15 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.62 (s, 6H,); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 161.4, 160.0, 158.7, 143.4, 136.6, 134.4, 132.9, 131.1, 129.0, 128.4, 128.2, 127.6, 127.5, 126.4, 125.8, 113.9, 113.9, 92.6, 56.0, 55.6, 55.4, 45.5; **IR (neat)** ν (cm^{-1}): 2999, 2936, 2835, 1601, 1508, 1463, 1246, 1204, 1115, 1036, 818; **HRMS** (ESI+, m/z): calculated for $C_{27}H_{27}O_4^+$ 415.1904, found 415.1908.

2-((3-fluorophenyl)(4-methoxyphenyl)methyl)-1,3,5-trimethoxybenzene (18k): Prepared from benzyl((3-fluorophenyl)(4-methoxyphenyl)methyl) sulfane and **TMB.** Pale yellow solid. Mp: 94 °C. **GP F**: (14.1 mg, 37%). **GP I**: (24.8 mg, 65%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.26 – 7.19 (m, 1H), 7.14 – 7.11 (m, 2H), 6.95 – 6.79 (m, 5H), 6.27 (s, 2H), 5.97 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.64 (s, 6H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 163.5 (d, *J* = 241.8 Hz), 161.5, 159.9, 158.9, 149.2, 135.9, 131.0 (3C), 129.8 (d, *J* = 8.7 Hz), 125.49 (d, *J* = 3.0 Hz), 116.1 (d, *J* = 22.2 Hz), 114.0, 113.6, 112.6 (d, *J* = 21.4 Hz), 92.5, 56.0, 55.6, 55.4, 45.1; **^{19}F NMR** (282 MHz, Acetone-d_6) δ 61.14; **IR (neat)** ν (cm^{-1}): 2936, 1609, 1589, 1510, 1464, 1247, 1221, 1116, 950, 765; **HRMS** (ESI+, m/z) calculated for $C_{23}H_{24}FO_4^+$ [M+H]+ 383.1653, found 383.1664.

1,3,5-trimethoxy-2-((4-methoxyphenyl)(4-(trifluoromethyl)phenyl) methyl)benzene (18l): Prepared from **17l** and **TMB**. Pale yellow solid. Mp: 126 °C. **GP F**: (10.8 mg, 25%). **GP I**: (32.9 mg, 76%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.15 (s, 2H), 6.02 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.60 (s,

6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.2, 158.9, 157.7, 149.2, 134.9, 130.2, 129.0, 127.3 (q, *J* = 32.5 Hz), 124.6 (q, *J* = 271.4 Hz), 124.3 (q, *J* = 4.2 Hz), 113.2, 112.8, 91.5, 55.6, 55.3, 55.2, 44.3; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.12 ; **IR (neat)** ν (cm^{-1}): 2931, 1607, 1510, 1465, 1325, 1162, 1117, 1067, 824; **HRMS** (ESI+, m/z): [M+H]+ calculated for $C_{24}H_{24}F_3O_4^+$ 433.1621, found 433.1624.

4-((4-chlorophenyl)(2,4,6-trimethoxyphenyl)methyl)phenol (18m): Prepared from **17m** and **TMB**. Colourless oil. **GP F**: (33.1 mg, 86%). **GP G**: (37.0 mg, 96%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.07 (s, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.10 (dd, *J* = 8.8, 0.8 Hz, 2H), 7.06 – 6.94 (m, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 6.25 (s, 2H), 5.91 (s, 1H), 3.80 (s, 3H), 3.63 (s, 6H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 161.4, 160.5, 159.9, 156.3, 145.1, 134.8, 131.3, 131.0, 128.1, 115.4, 113.8, 92.5, 56.0, 55.6, 44.7; **IR (neat)** ν (cm^{-1}): 3394, 2935, 2838, 1592, 1510, 1489, 1455, 1417, 1223, 1204, 1146, 1116, 812; **HRMS** (ESI+, m/z): [M+H]+ calculated for $C_{22}H_{22}ClO_4^+$ 385.1201, found 385.1204.

3-(phenyl(2,4,6-trimethoxyphenyl)methyl)-1H-indole (18n): Prepared from **17n** and **TMB** (1.5 equiv). Red oil. **GP G**: (12.8 mg, 34%). **GP I**: (7.5 mg, 20%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.42 – 7.34 (m, 2H), 7.28 – 7.12 (m, 6H), 7.06 – 7.98 (m, 1H), 6.92 (dd, *J* = 2.3, 0.9 Hz, 1H), 6.31 (s, 1H), 6.19 (s, 2H), 3.83 (s, 3H), 3.62 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 159.8, 159.1, 144.7, 136.1, 128.5, 128.0, 127.3, 125.0, 123.6, 121.4, 119.8, 119.0, 118.1, 114.4, 110.8, 91.8, 55.8, 55.3, 36.3; **IR (neat)** ν (cm^{-1}): 3417, 2936, 2837, 1603, 1493, 1456, 1417, 1337, 1221, 1204, 1149, 1061, 1033, 951, 813, 743, 700; **HRMS** (ESI+-, m/z): [M+K]+ calculated for $C_{24}H_{24}O_3KN^+$ 412.1310, found 412.1317.

2-(diphenyl(2,4,6-trimethoxyphenyl)methyl)-1H-indole (18o): Prepared from **17o** and **TMB** (1.5 equiv). Yellow oil. **GP G**: (23.0 mg, 51%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.30 – 7.00 (m, 15H), 6.20 (s, 2H), 5.56 (s, 1H), 3.88 (s, 3H), 3.52 (s, 6H).; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 160.8, 159.9, 142.8, 137.2, 135.9, 129.3, 129.2, 128.4, 126.5, 121.3, 120.2, 119.5, 110.8, 107.6, 104.4, 90.9, 55.6, 55.5, 48.9; **IR (neat)** ν (cm^{-1}): 3442, 2936, 1607, 1584, 1493, 1452, 1411, 1334, 1224, 1203, 1151, 1062, 1031, 950, 811, 729, 699; **HRMS** (ESI+, m/z): [M+Na]+ calculated for $C_{30}H_{27}O_3NaN^+$ 472.1883, found 472.1888.

3-((4-hydroxyphenyl)(2,4,6-trimethoxyphenyl)methyl)quinolin-2(1H)-one (18p): Prepared from **17p** and **TMB**. Pale yellow solid. Mp: 153 °C. **GP F**: (41.3 mg, 99%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 11.5 (s, 1H), 8.05 (s, 1H), 7.51 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.48 (s, 1H), 7.42 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.13 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.04 – 6.97 (m, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 3.62 (s, 6H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 163.6, 161.1, 160.3, 156.1, 138.8, 138.7, 137.5, 134.7, 130.7, 129.9, 128.3, 122.6, 121.0, 115.6, 115.3, 113.0, 92.6, 56.2, 55.5, 40.6; **IR (neat)** ν (cm^{-1}): 2935, 1645, 1607, 1512, 1222, 1117; **HRMS** (ESI+, m/z): [M+H]+ calculated for $C_{25}H_{24}NO_5^+$ 418.1649, found 418.1667.

6-fluoro-3-((4-hydroxyphenyl)(2,4,6-trimethoxyphenyl)methyl)quinolin-2(1H)-one (18q): Prepared from **17q** and **TMB**. Colourless oil. **GP F**: (40.5 mg, 93%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 11.50 (s, 1H), 8.10 (s, 1H), 7.46 (s, 1H), 7.41 – 7.30 (m, 1H), 7.29 – 7.19 (m, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.24 (s, 2H), 6.12 (s, 1H), 3.78 (s, 3H), 3.63 (s, 6H).

7-chloro-3-((4-hydroxyphenyl)(2,4,6-trimethoxyphenyl)methyl) quinolin-2(1H)-one (18r): Prepared from **17r** and **TMB**. Colourless oil. **GP F**: (44.8 mg,

99%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 10.87 (s, 1H), 8.04 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.12 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 6.23 (s, 2H), 6.06 (s, 1H), 3.79 (s, 3H), 3.62 (s, 6H).

1,3,5-trimethoxy-2-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)benzene (18s): Prepared from **17s** and **TMB**. Colourless oil. **GP F**: (20.2 mg, 52%). **GP I**: (34.1 mg, 88%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.47 – 7.30 (m, 7H), 6.83 – 6.80 (m, 2H), 6.27 (s, 2H), 5.77 (s, 1H), 3.82 (s, 6H), 3.80 (s, 3H), 3.74 (s, 3H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 161.6, 159.4, 159.0, 134.5, 132.3, 129.2 (3C), 128.4, 125.4, 113.9, 111.8, 92.3, 92.1, 81.6, 56.3, 55.6, 55.4, 31.4; **IR (neat)** ν (cm^{-1}): 2999, 2936, 2836, 1592, 1508, 1455, 1220, 1115, 1035, 950, 757; **HRMS** (ESI+, m/z): [M+H]+ calculated for $C_{25}H_{25}O_4^+$ 389.1747, found 389.1760.

6-methoxy-1-(2,4,6-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (18t): Prepared from **17t** and **TMB**. Colourless oil. **GP F**: (22.0 mg, 67%). **GP G**: (27.9 mg, 85%). **GP I**: (13.8 mg, 45%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.68 – 6.57 (m, 2H), 6.52 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.17 (s, 2H), 4.56 (dd, *J* = 11.2, 6.2 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.63 (brs, 6H), 2.96 – 2.74 (m, 2H), 2.18 -1.70 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.4, 159.2, 156.5, 138.1, 133.9, 128.0, 116.3, 112.9, 111.3, 91.7, 55.9, 55.2, 55.1, 33.9, 30.6, 29.0, 23.9. **IR (neat)** ν (cm^{-1}): 2935, 2835, 1605, 1590, 1497, 1464, 1417, 1223, 1203, 1149, 1116, 1039, 812. **HRMS** (ESI+, m/z): [M+H]+ calculated for $C_{20}H_{25}O_4^+$ 329.1747, found 329.1764.

4-(1-(2,4,6-trimethoxyphenyl)ethyl)phenol (18u): Prepared from **17u** and **TMB**. White solid. **GP F**: (24.5 mg, 85%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ

7.86 (s, 1H), 7.07 (dd, *J* = 8.7, 0.8 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 6.20 (s, 2H), 4.64 (d, *J* = 7.4 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 6H), 1.56 (d, *J* = 7.4 Hz, 3H).

4-(2-methyl-1-(2,4,6-trimethoxyphenyl)propyl)phenol (18v): Prepared from **17v** and **TMB**. White solid. **GP F**: (27.2 mg, 86%). Mp: 126 °C. **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.86 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 6.17 (s, 2H), 4.01 (d, *J* = 11.3 Hz, 1H), 3.80 (s, 6H), 3.74 (s, 3H), 3.04 – 2.80 (m, 1H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.76 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 160.5, 160.3, 159.7, 155.8, 137.1, 130.5, 115.2, 92.0, 56.0, 55.4, 49.1, 29.4, 23.0, 22.2; **IR (neat)** ν (cm^{-1}): 3396, 2961, 1604, 1510, 1465, 1223, 1203, 1149, 1132, 810; **HRMS** (ESI+, m/z): [M+H]+ calculated for $C_{19}H_{25}O_4^+$ 317.1747, found 317.1754.

4-(1-(2,4,6-trimethoxyphenyl)hexyl)phenol (18w): Prepared from **17w** and **TMB**. White solid. Mp: 89 °C. **GP F**: (22.2 mg, 63%). **GP I**: (15.5 mg, 45%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.86 (s, 1H), 7.24 – 7.04 (m, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 6.19 (s, 2H), 4.48 (dd, *J* = 9.5, 6.6 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 6H), 2.28 – 2.14 (m, 1H), 2.10 – 1.94 (m, 1H), 1.35 – 1.13 (m, 6H), 0.86 – 0.82 (m, 3H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 160.5, 160.1, 155.7, 137.8, 129.7, 115.1, 114.9, 92.2, 56.0, 55.4, 39.5, 33.1, 32.7, 29.1, 23.3, 14.4; **IR (neat)** ν (cm^{-1}): 3399, 2954, 2930, 2856, 1604, 1591, 1510, 1203, 1149, 1125; **HRMS** (ESI+, m/z): calculated for $C_{21}H_{29}O_4^+$ 345.2060, found 345.2071.

1,2,3-trimethoxy-4-(1-(2,4,6-trimethoxyphenyl)ethyl)benzene (18x): Prepared from **17x** and **TMB**. Clear oil. **GP F**: (22.1 mg, 61%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.04 (dd, *J* = 8.8, 8.8 Hz, 1H), 6.65 (d, *J* = 8.8, 8.8 Hz, 1H), 6.20 (s, 2H), 4.88 (q, *J* = 7.4 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.71 (s, 6H), 3.56 (s, 3H), 1.50 (d, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, Acetone-

d_6) δ 160.5, 160.1, 152.6, 152.5, 143.1, 133.3, 128.9, 127.5, 123. 7, 116.0, 107.7, 92.3, 60.5, 56.2, 56.0, 55.5, 28.9, 19.3; **IR (neat)** ν (cm^{-1}): 2936, 2836, 1590, 1492, 1459, 1414, 1290, 1224, 1203, 1150, 1122, 1025, 810; **HRMS** (ESI+, m/z): calculated for $C_{20}H_{27}O_6^+$ 363.1802, found 363.1824.

4-((2,4-dimethoxyphenyl)(phenyl)methyl)phenol (19aa): Prepared from **17a** and 1,3-dimethoxybenzene (3.0 equiv). White solid. Mp: 121 °C. **GP F**: (31.0 mg, 97%). **GP I**: (16.7 mg, 52%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 – 7.23 (m, 2H), 7.19 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.77 – 6.68 (m, 3H), 6.47 (d, *J* = 2.1 Hz, 1H), 6.40 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.77 (s, 1H), 4.67 (s, 1H), 3.79 (s, 3H), 3.70 (s, 3H). **^{13}C NMR** (75 MHz, Acetone-d_6) δ 160. 6, 158.9, 156.5, 145.9, 135.9, 131.3, 131.1, 130.0, 128.8, 126.6, 126.2, 115.7, 105.0, 99.3, 55.9, 55.5, 49.2; **IR (neat)** ν (cm^{-1}): 3391, 2939, 1597, 1511, 1491, 1461, 1250, 1091, 1034, 700; **HRMS** (ESI+, m/z): calculated for $C_{21}H_{24}NO_3^+$ 338.1751, found 338.1754.

4-(phenyl(2,3,4-trimethoxyphenyl)methyl)phenol (19ab): Prepared from **17a** and 1,2,3-trimethoxybenzene (1.5 equiv). Yellow oil. **GP F**: (24.2 mg, 69%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 – 7.16 (m, 3H), 7.11 – 7.08 (m, 2H), 6.99 – 6.94 (m, 2H), 6.76 – 6.71 (m, 2H), 6.54 (q, *J* = 8.7 Hz, 2H), 5.77 (s, 1H), 4.85 (br s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.51 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.9, 152.3, 151.7, 144.4, 142.3, 136.3, 131.0, 130.5, 129.3, 128.2, 126.1, 124.3, 115.0, 106.7, 60.7, 60.6, 55.9, 49.1; **IR (neat)** ν (cm^{-1}): 3387, 2940, 1600, 1511, 1492, 1463, 1276, 1171, 1094, 701; **HRMS** (ESI+, m/z): calculated for $C_{22}H_{23}O_4^+$ 351.1591, found 351.1581.

tert-butyl (2-((4-hydroxyphenyl)(phenyl)methyl)-3,5-dimethoxyphenyl)carbamate (19ac): Prepared from **17a** and tert-butyl 3,5-

dimethoxyphenylcarbamate (3.0 equiv). Clear oil. **GP F**: (25.2 mg, 34%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.30 (s, 1H), 7.33 – 7.20 (m, 3H), 7.15 – 7.12 (m, 2H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.96 – 6.93 (m, 2H), 6.81 – 6.78 (m, 2H), 6.56 (br s, 1H), 6.39 (d, *J* = 2.44 Hz, 1H), 6.15 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 1.32 (s, 9H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 160.5, 159.4, 156.9, 153.4, 143.8, 139.6, 133.5, 130.6, 129.6, 129.3, 127.1, 116.2, 101.1, 95.4, 79.9, 56.3, 55.5, 45.2, 28.3; **IR (neat)** ν (cm^{-1}): 3389, 2976, 2934, 1730, 1703, 1611, 1592, 1512, 1451, 1239, 1159, 1049, 831; **HRMS** (ESI+, m/z): calculated for $C_{28}H_{32}N_2NaO_5^+$ 499.2203, found 499.2216.

di-tert-butyl (4-((4-hydroxyphenyl)(phenyl)methyl)-1,3-phenylene) dicarbamate (19ad): Prepared from **17a** and di-tert-butyl 1,3-phenylenedicarbamate (3.0 equiv). Colourless oil. **GP F**: (16.7, 34%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.3 Hz, 1H), 7.31 – 7.19 (m, 3H), 7.12 – 7.04 (m, 3H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.73 – 6.65 (m, 3H), 6.55 (brs, 1H), 6.11 (brs, 2H), 5.40 (s, 1H), 1.49 (s, 9H), 1.42 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.80, 153.4, 152.9, 142.5, 137.3, 136.0, 133.6, 130.4, 130.3, 129.9, 129.3, 128.6, 126.7, 115.5, 114.6, 113.6, 80.6, 51.0 (2C), 28.3, 28.2; **IR (neat)** ν (cm^{-1}): 3336, 29778, 1695, 1593, 1513, 1367, 1232, 1152, 1053, 1029, 700; **HRMS** (ESI+, m/z): calculated for $C_{29}H_{34}N_2NaO_5^+$ 513.2360, found 513.2374.

tert-butyl (2-((4-hydroxyphenyl)(phenyl)methyl)-3-methoxyphenyl)carbamate (19ae): Obtained from **17a** and tert-butyl (3-methoxyphenyl)carbamate (3.0 equiv). Yellow solid. Mp: 169 °C. **GP F:** (12.6 mg, 31%). **^{1}H NMR** (300MHz, $CDCl_3$) δ 7.19 – 7.07 (m, 4H), 6.99 (d, *J* = 6.8 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 6.56 (d, *J* = 8.6 Hz, 1H), 6.46 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.43 (brs, 1H), 5.68 (s, 1H), 5.53 (brs, 1H), 3.61 (s, 3H), 1.44 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.6, 154.1, 153.0,

144.5, 138.0, 136.2, 130.6, 130.5, 129.5, 128.2, 127.9, 126.0, 115.1, 110.1, 102.1, 80.7, 55.8, 48.5, 28.5; **IR (neat)** ν (cm^{-1}): 3269, 2979, 1679, 1600, 1532, 1510, 1448, 1412, 1366, 1289, 1250, 1150, 1116, 1060, 1035, 972, 814, 701; **HRMS** (ESI^+, m/z): calculated for $C_{27}H_{30}N_2NaO_4^+$ 469.2098, found 469.2091.

tert-butyl (2-((4-hydroxyphenyl)(phenyl)methyl)-5-methoxyphenyl) carbamate (19ae'): Prepared from **17a** and tert-butyl (3-methoxyphenyl)carbamate (3.0 equiv). Yellow oil. **GP F**: (13.8 mg, 34%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (brs, 1H), 7.24 – 7.13 (m, 4H), 7.00 – 6.98 (m, 2H), 6.86 – 6.83 (m, 2H), 6.68 – 6.65 (m, 2H), 6.58 - 6.55 (m, 1H), 6.48 – 6.44 (m, 1H), 6.07 (brs, 1H), 5.32 (s, 1H), 3.70 (s, 3H), 1.36 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.7, 154.2, 153.1, 144.6, 138.1, 136.3, 130.7, 130.6, 129.6, 128.3, 128.0, 126.1, 115.2, 110.2, 102.2, 80.8, 55.9, 48.6, 28.6.; **IR (neat)** ν (cm^{-1}): 3391, 2976, 2930, 1694, 1612, 1584, 1511, 1466, 1366, 1229, 1152, 1050, 1029, 744, 699; **HRMS** (ESI^+, m/z): calculated for $C_{27}H_{30}N_2NaO_4^+$ 469.2098, found 469.2089.

4-((5-bromo-1H-indol-3-yl)(phenyl)methyl)phenol (19af): Prepared from **17a** and 5-bromo-1H-indole (3.0 equiv). Red oil. **GP G**: (29.4 mg, 77%). **^{1}H NMR** (300 MHz, CD_3CN): δ 9.25 (s, 1H), 7.36 – 7.16 (m, 8H), 7.06 (d, J = 8.4 Hz, 2H), 6.84 (s, 1H), 6.75 (d, J = 8.4Hz, 2H), 6.68 (dd, J = 2.4, 0.9 Hz, 1H), 5.56 (s, 1H); **^{13}C NMR** (75 MHz, CD_3CN): δ 156.3, 145.5, 136.6, 136.2, 133.4 130.7, 129.6, 129.3, 127.2, 126.7, 125.1, 122.6, 120.0, 116.0, 114.3, 112.5, 48.5; **IR (neat)** ν (cm^{-1}): 3426, 3309, 1598, 1509, 1451, 1329, 1249, 1214, 1170, 1101, 801, 737; **HRMS** (ESI+, m/z): calculated for $C_{13}H_{11}O^+$ 183.0804, found 183.0803.

4-((5-nitro-1H-indol-3-yl)(phenyl)methyl)phenol (19ag): Prepared from **17a** and 5-nitro-1H-indole (3.0 equiv). Yellow solid. Mp: 269 °C. **GP G**: (24.9 mg, 72%). **^{1}H NMR** (300 MHz, CD_3CN) δ 9.67 (s, 1H), 8.07 (d, *J* = 2.3 Hz, 1H), 7.99 (dd, *J* =8.9, 2.3 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.37 – 7.18 (m, 5H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.89 (s, 1H), 6.85 (dd, *J* = 2.3, 1.1 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 5.68 (s, 1H). **^{13}C NMR** (75 MHz, CD_3CN): δ 156.5, 145.2, 142.0, 141.0, 135.9, 130.7, 129.6, 129.4, 128.7, 127.4, 127.2, 122.8, 118.1, 117.3, 116.1, 112.7, 48.3; **IR (neat)** ν (cm^{-1}): 3534, 3291, 1612, 1510, 1470, 1450, 1429, 1262, 1160, 1089, 799, 737, 700; **HRMS** (ESI+, m/z): calculated for $C_{21}H_{17}N_2O_3^+$ 345.1234, found 345.1227.

2-methoxy-5-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)thiophene (19ta): Prepared from **17t**[1] and 2-methoxythiophene (3.0 equiv). Colourless oil. **GP G**: (12.8 mg, 49%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.04 (d, *J* = 9 Hz, 1H), 6.69 (d, *J* = 9 Hz, 1H), 6.66 – 6.63 (m, 1H), 6.28 (d, *J* = 3 Hz, 1H), 5.98 (d, *J* = 3 Hz, 1H), 4.17 (t, *J* = 6 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.90 – 2.70 (m, 2H), 2.18 – 2.08 (m, 1H), 2.00 – 1.85 (m, 2H), 1.83 – 1.68 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ (ppm) 164.6, 157.9, 138.2, 137.4, 131.0, 130.7, 122.0, 113.3, 112.0, 102.5, 60.1, 55.2, 40.2, 33.3, 29.8, 20.5; **IR (neat)** ν (cm^{-1}): 2930, 2832, 1724, 1607, 1559, 1430, 1323, 1250, 1202, 1151, 1037, 997, 818, 769, 717; **HRMS** (ESI+, m/z): calculated for $C_{16}H_{19}O_2S^+$ 275.1100, found 275.1100.

4-((1H-indazol-1-yl)(phenyl)methyl)phenol (19ah): Prepared from **17a** and indazole (1.5 equiv). Yellow oil. **GP F**: (29.4 mg, 98%). **GP G**: (24.0 mg, 80%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.25 (m, 5H), 7.23 – 7.14 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.99 (s, 1H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.15 (s, 1H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 157.9, 141.9, 141.1, 134.0, 132.0, 130.8, 129.1, 129.0, 128.2, 126.9, 125.3, 121.7, 121.5, 115.9,

110.7, 66.1; **IR (neat)** ν (cm^{-1}): 3216, 3062, 2929, 1715, 1614, 1598, 1514, 1450, 1237, 1173, 909, 740, 698; **HRMS** (ESI+, m/z): calculated for $C_{20}H_{17}N_2O^+$ 301.1335, found 301.1342.

4-(phenyl(1H-pyrazol-1-yl)methyl)phenol (19ai): Prepared from **17a** and imidazole (3.0 equiv). Colourless oil. **GPF**: (23.3 mg, 93%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.45 (s, 1H), 7.51 – 7.48 (m, 2H), 7.37 – 7.25 (m, 3H), 7.13 – 7.04 (m, 4H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.77 (s, 1H), 6.26 (t, *J* = 2.1 Hz, 1H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 158.0, 142.1, 139.8, 132.0, 130.7, 130.2, 129.2, 128.7, 128.3, 116.1, 105.8, 69.5; **IR (neat)** ν (cm^{-1}): 3124, 1614, 1515, 1454, 1400, 1242, 1172, 1056, 795, 739. **HRMS** (ESI+, m/z): calculated for $C_{13}H_{11}O^+$ 183.0804, found 183.0806.

tert-butyl ((4-hydroxyphenyl)(phenyl)methyl)carbamate (19aj): Prepared from **17a** and tert-butyl carbamate (3.0 equiv). Colourless oil. **GP F**: (21.8 mg, 73%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 – 7.16 (m, 5H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 5.83 (brs, 1H), 5.56 (s, 1H), 5.13 (brs, 1H), 1.44 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.3, 153.5, 142.5, 134.4, 128.8 (3C), 127.5, 127.4, 115.7, 77.5, 58.2, 28.6; **IR (neat)** ν (cm^{-1}): 3333, 2978, 2932, 1682, 1513, 1366, 12447, 1164, 699; **HRMS** (ESI+, m/z): calculated for $C_{20}H_{24}N_2NaO_3^+$ 363.1679, found 363.1683.

benzyl ((4-hydroxyphenyl)(phenyl)methyl)carbamate (19ak): Prepared from **17a** and benzylcarbamate (3.0 equiv). White solid. Mp: 123 °C. **GP F**: (27.3 mg, 82%). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.30 (s, 1H), 7.37 – 7.23 (m, 10H), 7.18 – 7.15 (m, 2H), 6.81 – 6.76 (m, 2H), 5.94 (d, *J* = 8.9 Hz, 1H), 5.08 (s, 2H), 5.04 (s, 1H); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 157.4, 144.2, 138.2, 134.5, 129.5, 129.18, 129.14, 128.64, 128.58, 128.1, 127.7, 116.0, 66.7, 66.3, 59.2; **IR**

(neat) ν (cm^{-1}): 3317, 3031, 1692, 1614, 1597, 1513, 1454, 1341, 1228, 1040, 738, 697; **HRMS** (ESI+, m/z): calculated for $C_{21}H_{20}NO_3^+$ 334.1438, found 334.1438.

4-(((4-bromophenyl)amino)(phenyl)methyl)phenol (19tb): Prepared from **17t**[1] and 4-bromoaniline (3.0 equiv). Yellow oil. **GP G**: (18.4 mg, 52%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.14 (m, 3H), 6.75 – 6.62 (m, 1H), 6.59 – 6.55 (m, 1H), 6.46 (d, *J* = 8.9 Hz, 2H), 4.46 (d, *J* = 4.2 Hz, 1H), 3.79 (s, 1H), 3.72 (s, 3H), 3.73 – 3.62 (m, 1H), 2.88 – 2.54 (m, 2H), 1.89 – 1.65 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.9, 146.6, 139.2, 132.3, 130.7, 130.2, 114.6, 113.6, 112.8, 108.6, 55.5, 50.8, 29.9, 28.8, 19.4; **IR (neat)** ν (cm^{-1}): 3404, 2931, 2834, 1591, 1396, 1311, 1245, 1179, 1155, 1037, 811; **HRMS** (ESI+, m/z) calculated for $C_{11}H_{13}O^+$ 161.0961, found 161.0958.

1-azido-6-methoxy-1,2,3,4-tetrahydronaphthalene (19tc): Prepared from **17t** and azidotrimethylsilane (3.0 equiv). Yellow oil. **GP F**: (15.6 mg, 77%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.5 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 4.57 – 4.52 (m, 1H), 3.79 (s, 3H), 2.90 – 2.65 (m, 3H), 2.05 – 1.90 (m, 3H), 1.85 – 1.70 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 159.4, 139.0, 130.6, 126.2, 114.0, 112.5, 59.3, 55.4, 29.5, 29.3, 18.9; **IR (neat)** ν (cm^{-1}): 3322, 2934, 2836, 1712, 1607, 1501, 1255, 1234, 1156, 1123, 1110, 1037, 946, 854, 810, 773, 699; **HRMS** (ESI+, m/z): calculated for $C_{11}H_{13}O^+$ 161.0961, found 161.0950.

1-((4-methoxyphenyl)(phenyl)methyl)-1H-indazole (19tb): Prepared from **17d** and 4-indazole (3.0 equiv). Colourless oil. **GP I**: (19.0 mg, 60%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.17 (m, 3H), 7.06 – 6.97 (m, 7H), 6.82 (d, J = 8.4 Hz, 2H), 3.74 (s,

3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.8, 149.2, 139.6, 131.2, 130.1, 129.0, 128.4, 128.2, 126.3, 123.4, 122.0, 121.7, 120.6, 118.0, 114.4, 70.8, 55.6; **IR (neat)** ν (cm^{-1}): 3060, 2031, 2836, 1610, 1512, 1453, 1390, 1330, 1304, 1176, 1129, 1030, 911, 811, 785, 757, 732, 698; **HRMS** (ESI+, m/z): calculated for $C_{21}H_{19}N_2O^+$ 315.1492, found 315.1493.

5-bromo-3-((4-methoxyphenyl)(phenyl)methyl)-1H-indole (19da): Prepared from **17d** and 5-bromo-1H-indole (3.0 equiv). **GP I**: (23.2 mg, 59%). Colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.37 (s, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.19 (m, 5H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.57 (s, 1H), 5.56 (s, 1H), 3.79 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.3, 144.1, 135.9, 135.6, 130.1, 129.1, 129.0, 128.6, 126.6, 125.4, 125.3, 122.6, 120.3, 114.0, 113.0, 112.7, 55.5, 47.9; **IR (neat)** ν (cm^{-1}): 3424, 3027, 1599, 1460, 1250, 1176, 1097, 1031, 885, 796, 701; **HRMS** (ESI-, m/z): calculated for $C_{22}H_{17}NOBr^-$ 390.0494, found 390.0485.

((benzylsulfinyl)methylene)dibenzene (18f'): Prepared according to **GP F** from **17a** and **TMB** (1.5 equiv). White-brown solid (20.2 mg, 66%). Mp: 131 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 – 7.33 (m, 13H), 7.24 – 7.18 (m, 2H), 4.73 (s, 1H), 3.88 (d, *J* = 13.2 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 136.1, 134.7, 130.5, 130.3, 129.7, 129.4, 128.9, 128.8, 128.4, 128.4, 70.1, 56.5. **IR (neat)** ν (cm^{-1}): 3060, 3031, 1597, 1583, 1494, 1451, 1404, 1084, 1074, 1036, 1002, 918, 879, 765, 751; **HRMS** (ESI+, m/z): calculated for $C_{20}H_{18}NaOS^-$ 329.0971, found 329.0979.

3-((benzylsulfinyl)(phenyl)methyl)phenol (18c'): Prepared according to **GP F** from **18c** and **TMB** (1.5 equiv). White-brown solid (26.0 mg, 81%). Mp: 148 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.50 – 7.30 (m, 16H), 7.25 – 7.10 (m, 6H), 7.02

(t, J = 3 Hz, 1H), 6.94 (t, J = 3 Hz, 1H), 6.91 (d, J = 9 Hz, 1H), 6.87 (d, J = 9 Hz, 1H), 6.75 – 6.66 (m, 2H), 5.82 (s, 1H), 4.78 (s, 1H), 4.74 (s, 1H), 3.96 – 3.72 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 157.5, 157.4, 157.1, 136.8, 135.8, 135.7, 134.5, 130.5, 130.4, 130.3, 130.2, 129.9, 129.7, 129.5, 129.0, 128.9, 128.8, 128.6, 128.6, 128.5, 120.8, 120.2, 116.9, 116.2, 116.0, 107.5, 70.9, 70.4, 56.4, 56.4; **IR (neat)** ν (cm^{-1}): 3172, 1697, 1596, 1494, 1453, 1285, 1218, 11.05, 1021, 733; **HRMS** (ESI-, m/z): calculated for $C_{21}H_{19}O_4S^-$ 367.1007, found 367.0989.

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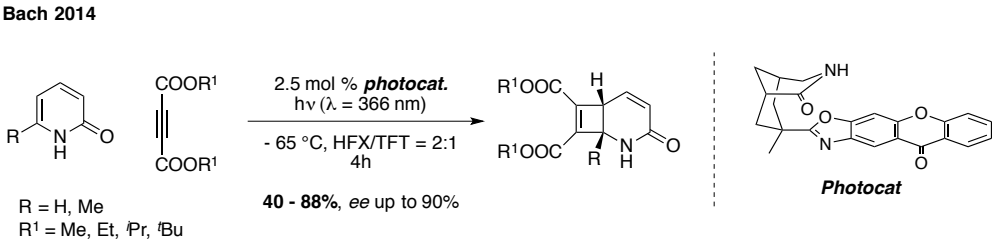
8 Tetracyclization of Dienynes via Photo/Redox Catalysis

8.1 Introduction

The last decade saw the rise of visible light as a promoter of unique reactivities together with the development of an ample mix of easily tunable photocatalysts (PCs). Under the energy transfer mechanism, the energetic level of the excited photosensitizer has to be compatible with the gap between the singlet and triplet state of the substrate. [145,198,201,223,270–273] A wide number of papers ware already reported in [2+2] cycloaddition to synthesize cyclobutanes and cyclobutenes. [274,275]

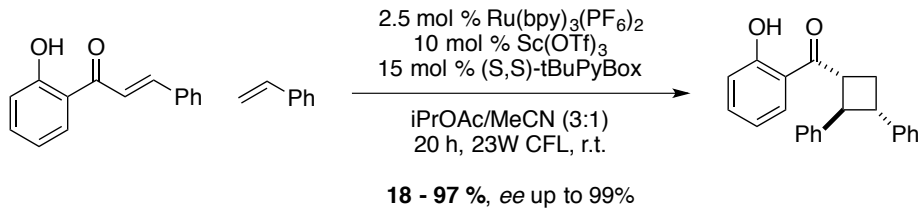
Bach in 2014 reported the first intermolecular photocatalized [2+2] enantioselective cycloaddition. [276] A chiral organocatalyst has proven able to activate a pyridone that can undergoes [2+2] with an internal alkyne.



Scheme 51 Selected example of enantioselective organo photocatalyzed [2+2] cyloaddition

More recently Yoon reported an enantioselective [2+2] cycloaddition employing a photosensitizer, a chiral ligand and a Lewis acid as catalysts in an intermolecular approach. [277] The Lewis acid lowers the triplet state energy of the substrate, greatly enlarging the scope of the reaction.

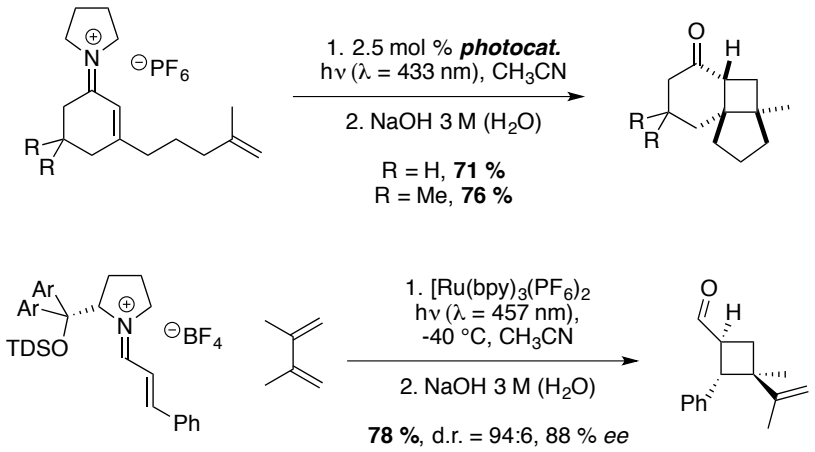
Yoon 2017



Scheme 52 Selected example of ruthenium photocatalyzed [2+2] cycloaddition

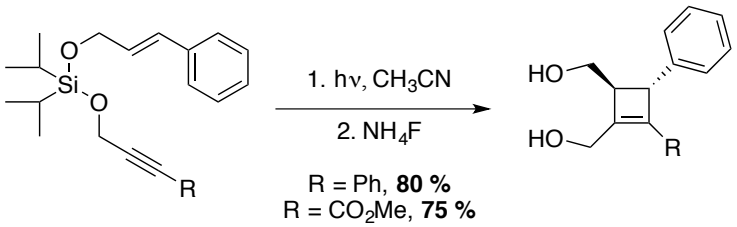
In 2018 Bach illustrated the [2+2] cycloaddition of eniminiums. [278] Eniminium cations have lower triplet state energy compared to enones. The use of proline allows and enantioselective variant of the method.

Bach 2018



Scheme 53 Selected examples of inter- and intramolecular [2+2] cycloadditions

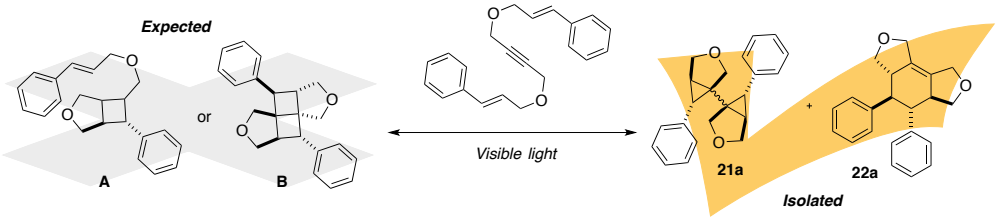
This strategy can be extended to dienes, trienes and enynes. Few examples only ware reported for the latter, which gave fused bicyclic compounds with a cyclobutene ring. [279] Alkynes can often remain unchanged due to the instability of their triplet state. [280,281] Just one example of photomediated reaction using 1,8-enynes has been reported. [282]



Scheme 54 Example of enyne photocycloaddition

8.2 Results and discussion

During our investigation on Pd_3^+/photoredox cascade reaction using dienynes, we were surprised by the appearance of NMR resonances that were unusually shifted upfield. The formation of a product responsible of these signals soon revealed to be caused by light and PC only. We initially speculate that these signals could be due to **A**, formed via enyne [2+2], or to ladderanoid tetracycle **B**, resulting from a dual [2+2] in the presence of a second styryl fragment on **20**. Much to our surprise, we were able to isolate two products, **21** and **22**, which turned out to be orthogonal to any reasonable expectation.



Product **21** presents two tethered 3.1.0 bicyclic units. It presents six contiguous stereocenters, including two quaternary carbons. The product is retrieved as ca. 1:1 mixture of just two out of its 32 potential diastereoisomers. They differ from the relative arrangement of the head bridging carbons, the configuration of each cyclopropyl ring being fixed. Product **22** is a fused tricycle with a central cyclohexene presenting four contiguous stereocenters. The product is retrieved as ca. 1:1 mixture of just two out of its 8 potential diastereoisomers. They differ from the relative arrangement of the two benzylic moieties, the configuration of each original alkene unit being fixed. The structure of **21** and **22** has been assigned via X-ray analyses.

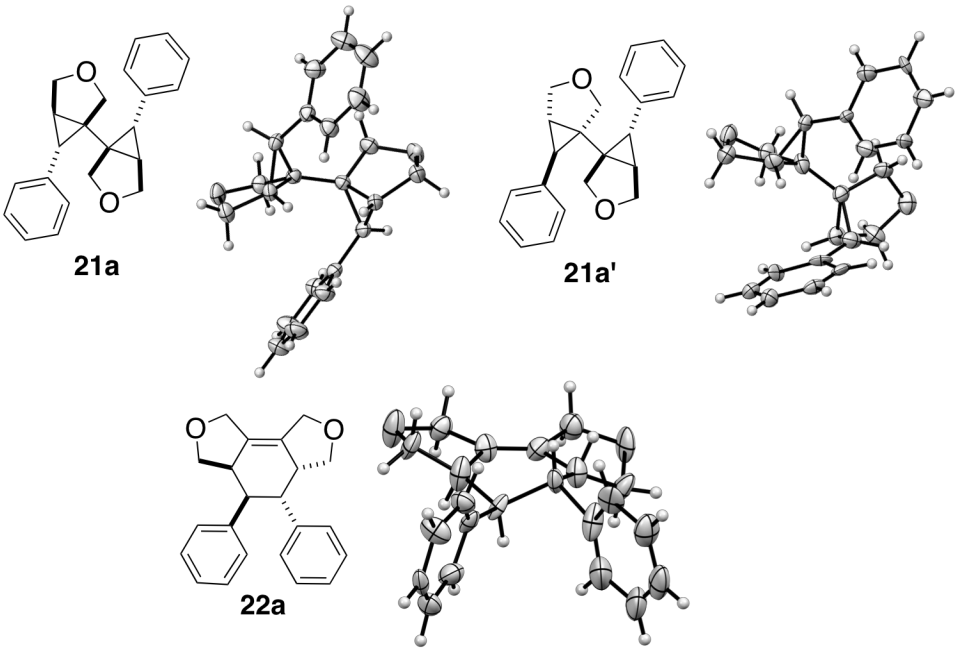
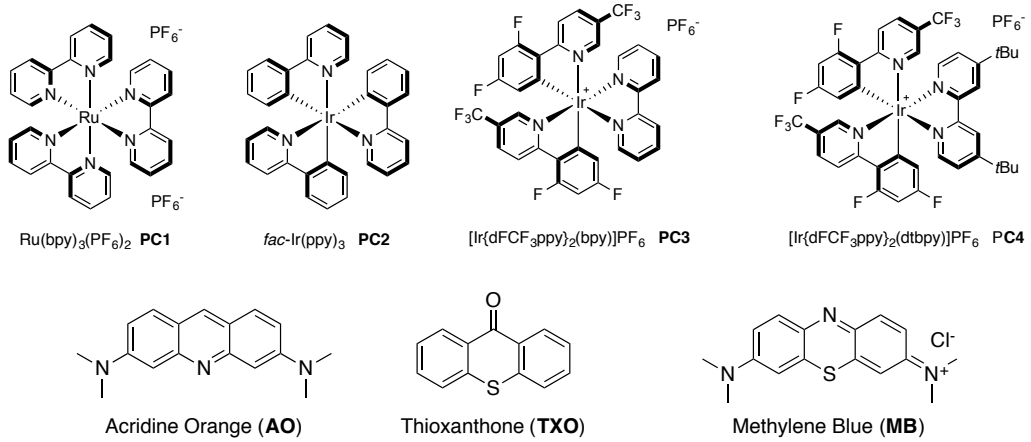
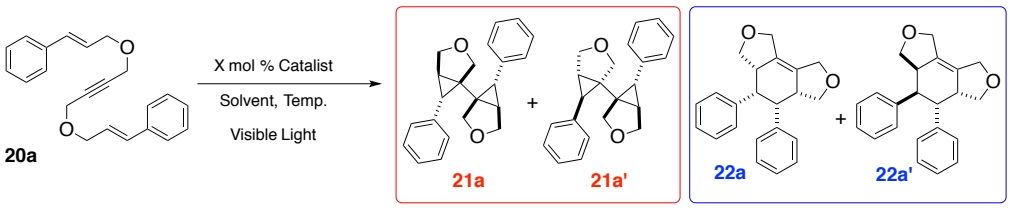


Figure 12 X-Ray structrures of products

We thus decided to optimize reaction conditions intrigued by this tetracyclization and by the formal dicarbenoid behavior of the carbon atoms of the alkyne, which, to the best of our knowledge, has not been previously observed under photocatalytic conditions. [184,283–285]



Scheme 55: Photocatalyst



Entry[a]	Catalyst	Solvent	Cyclization yield (%)[b]	21/22 ratio[b]
1	**PC1**	DCM	30	50/50
2	**PC1**	CH_3CN	35	50/50
3	**PC1**	DMF	60	56/44
4[c]	**PC1**	DMF	traces	--
5	**PC1**	$MeNO_2$	--	--
6	**PC2**	DMF	--	--
7[d]	**PC1**	DMF	75	55/45
8[d]	**PC3**	DMF	90	61/39
9[d]	**PC4**	DMF	91	62/38
10[d]	**MB**	DMF	--	--
11[d]	**AO**	DMF	--	--
12[d]	**TXO**	DMF	--	--
13	**MB + AO**	DMF	--	--

[a] Conditions: 0.2 mmol scale of **20a** (0.2 M), 2.5 mol % of catalyst, in a water bath at 45 °C irradiated with a white 7W LED strip for 24 hours. [b] Determined by ^{1}**H NMR** with 1,2-dibromomethane as internal standard. [c] Under oxygen atmosphere. [d] Reaction performed in standard 0.4 mm NMR tubes

Products **21a** and **22a** form in a 50/50 ratio in DCM (entry 1, 30% combined yield). Increasing the polarity of the solvent proved beneficial (entries 2-3) and the use of DMF favored the formation of **21** over that of **22** (56/44 ratio). Reactivity is completely inhibited by the presence of oxygen or $MeNO_2$, which can both quench Ir-photocatalyzed reactions that occurs *via* energy transfer (entries 4-5). [286] Use of popular PC2, which has a lower energy triplet, followed suit. An increase in the surface/volume ratio of the reactor, by using standard NMR tubes, pushed the combined yield to 75% (entry 7). The mass balance is completed by the recovery of the (*Z*)-isomer of **20** and no other species form. Use of PC3 and PC4 enabled both a better yield and a higher ratio of **21** (entries 8-9). The NMR spectra of crude mixtures is surprisingly clean. Indeed, each product can be recognized directly from the spectrum (^{1}H NMR of entry 9).

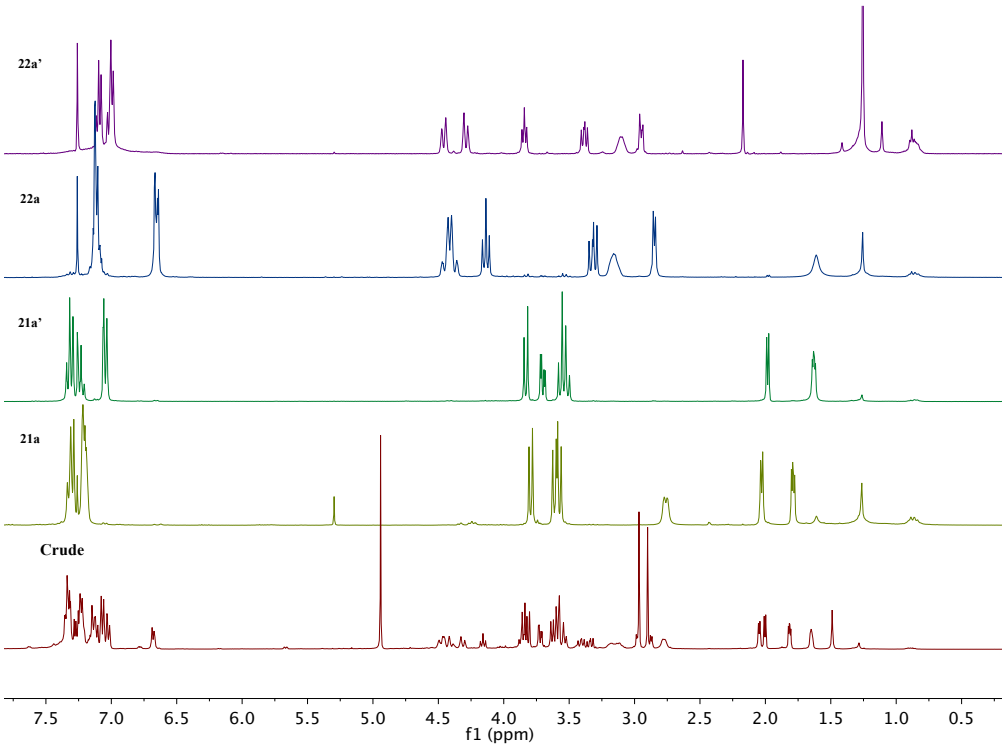
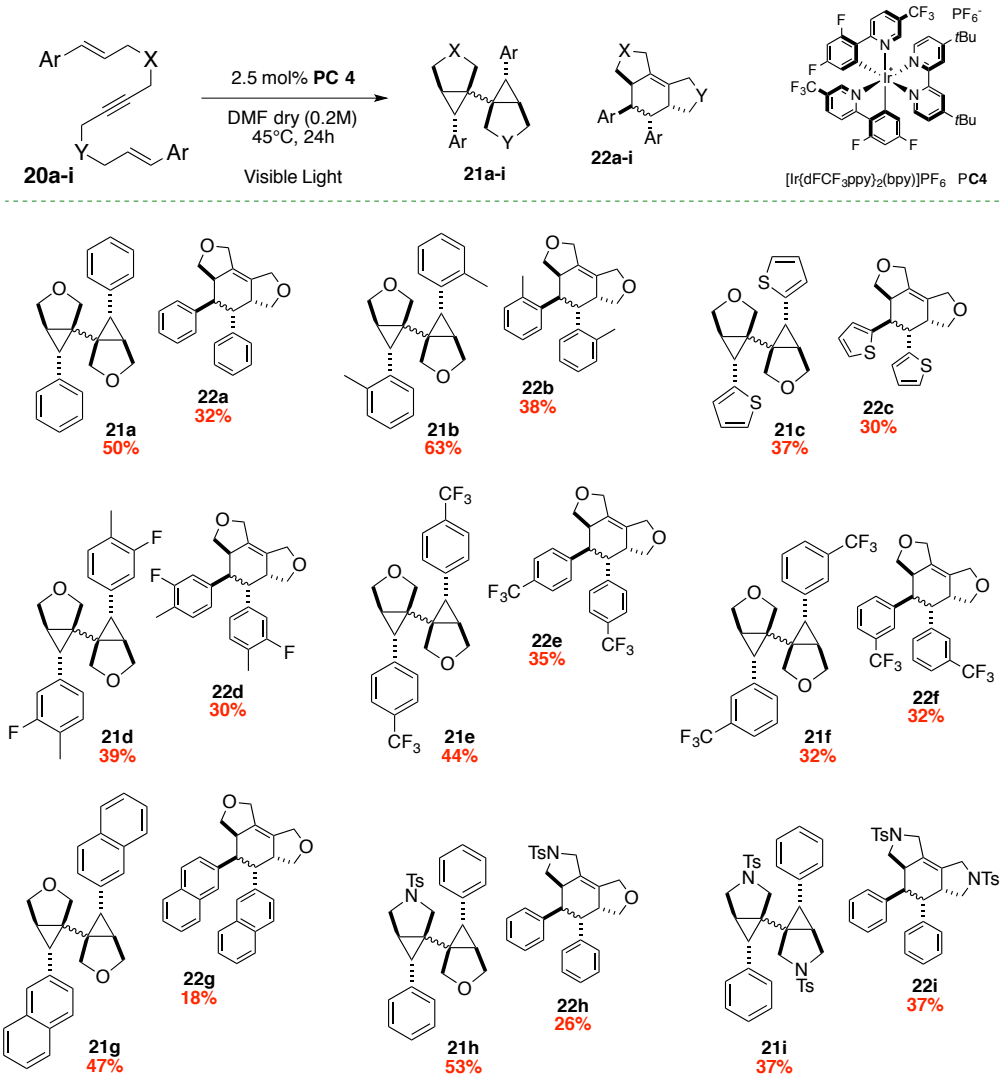


Figure 13 ^{1}H NMR spectra of products and **^{1}H NMR** of reaction crude of Entry 9

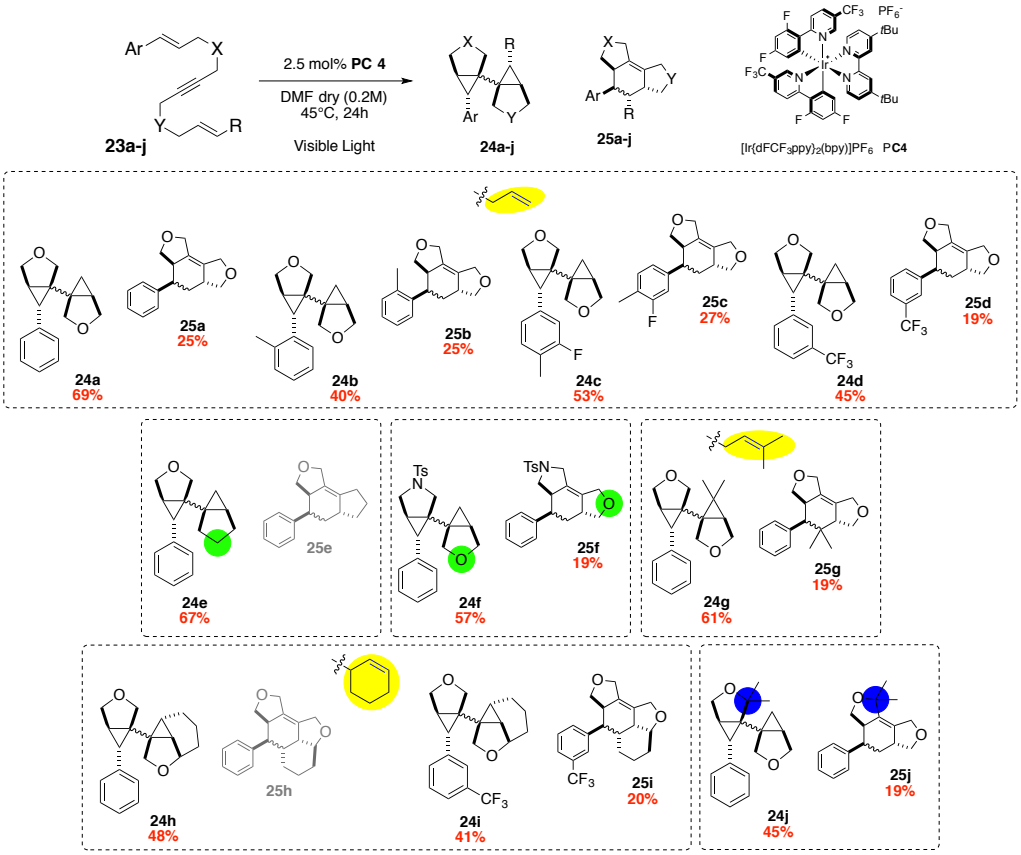
We then studied the generality of the reaction, preparing a library of aryldienynes in general *via* tandem Heck/Tsuji-Trost allylations. [287,288] The photocatalytic method can be applied to symmetric dienynes with a variety of aromatic rings on their alkene arms (Scheme 50, **a**-**i**). This includes *ortho*-substituted aryls, thiophene, differently fluorinated aromatics and fused polycycles such as 2-naphtalene. The nature of the spacer among insaturations can be modified, accessing the corresponding *N*-containing polyheterocycles (**h**, **j**). [289] In all cases, products were separated by preparative TLCs. The formation of tetracycles **21** (32-63%) is always slightly favored over that of tricycles **22** (18-37%). Both invariably form as a ca. 1:1 mixture of diastereomers.



Scheme 56 Scope of symmetric dienynes

We then tested non-aromatic alkene group (**j**-**s**) (Scheme 51). In these cases, formation of **2** (40-69%) results more favored over that of **3** (0-27%). Their structural features paralleled previous examples. An allyl group is well tolerated (**j**-**o** and **s**). Both **2b** and **2k** forms in higher yield compared to **2a** (63, 69 and 50%, respectively) while **2i** is retrieved in a lower 40% yield. This shows that the

impact on reactivity of the terminal alkene is interconnected with the substitution of the styryl fragment.



Scheme 57 Scope of allyl fragment

Fluorinated substrates performed slightly better in combination with an allyl group. Gratifyingly, it is possible to assemble bare carbobicyclic units (**24e**, 67%) and nitrogen containing ones (**24f**, 57%). No **25e** formed in the former case. A trisubstituted alkene can be used, as witnessed by **24g** (61%), which thus present a third contiguous all-carbon quaternary center in its structure. Cyclic alkenes too can be reacted, leading to the corresponding penta- and tetracyclic products **24h-i** and **25h-i** respectively. Using racemic substrates **23h** and **23i**, just 2 out of the 64 potential diastereomers of the corresponding pentacycles **2** were observed.

The same trend is observed in tetracycle **25i** (20%), while **25h** did not form at all. These results indicate that each enantiomer of the reagent reacted in a stereospecific fashion. [290] Finally, substitution at the propargylic position has been tested and lead to formation of **24j** and **25j**, which present three contiguous quaternary carbons each.

Figure 14 presents the limitations of this reaction. These substrates gave no conversion.

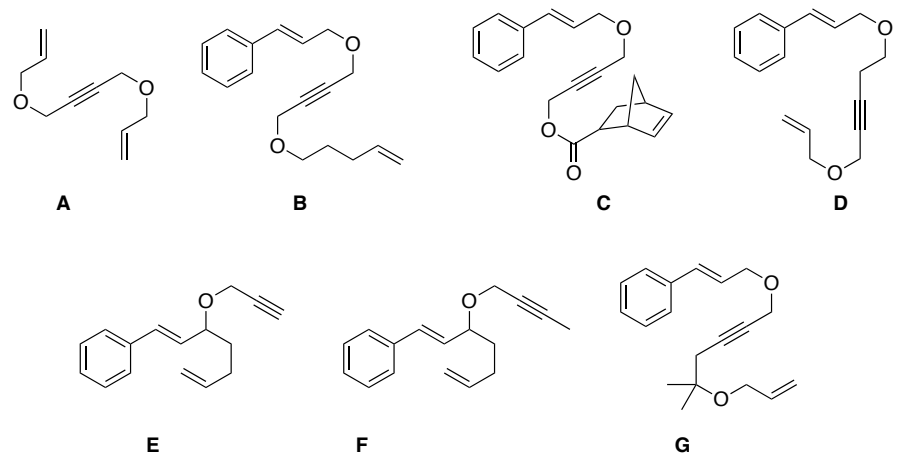


Figure 14 Unsuccessful substrates

We performed the reaction of **20a** and alternate periods of light and dark. The yields of products **21** and **22** ware determined by ^{1}H NMR. The experiments showed that conversion cease in the absence of irradiation. Complete conversion of **20a** to **21** and **22** was observed after 24 and 16 hours using 2.5 and 5 mol% of photocatalyst respectively.

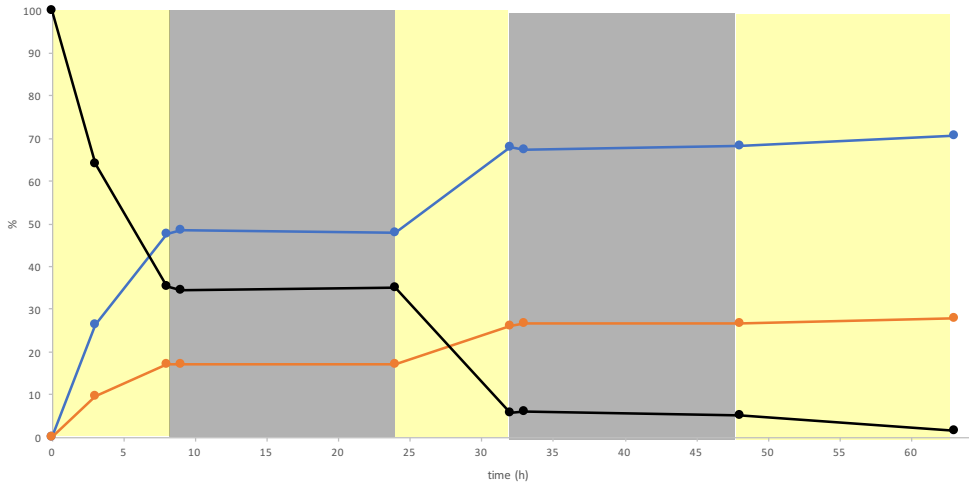


Figure 15: 2.5 mol % of **PC4**, Yield of Blue line **21a**, Yield of Orange line **22a**, Conversion of **20a**

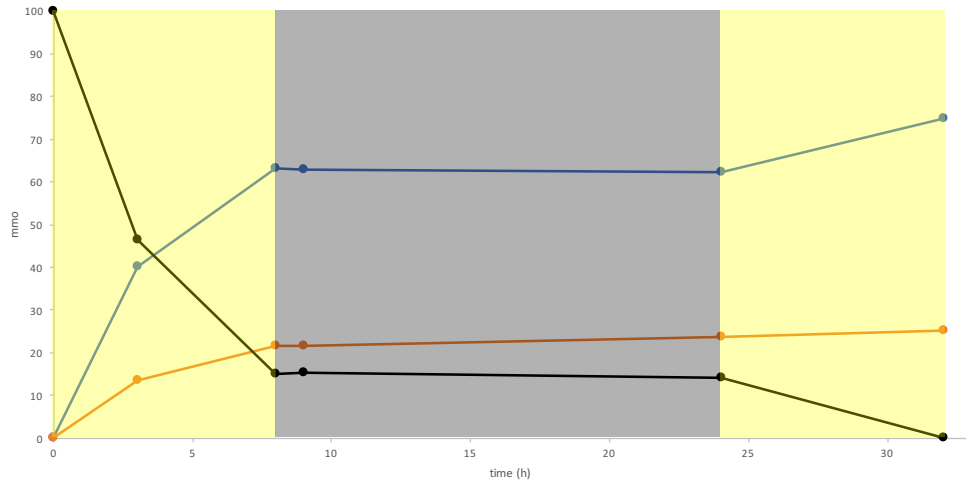


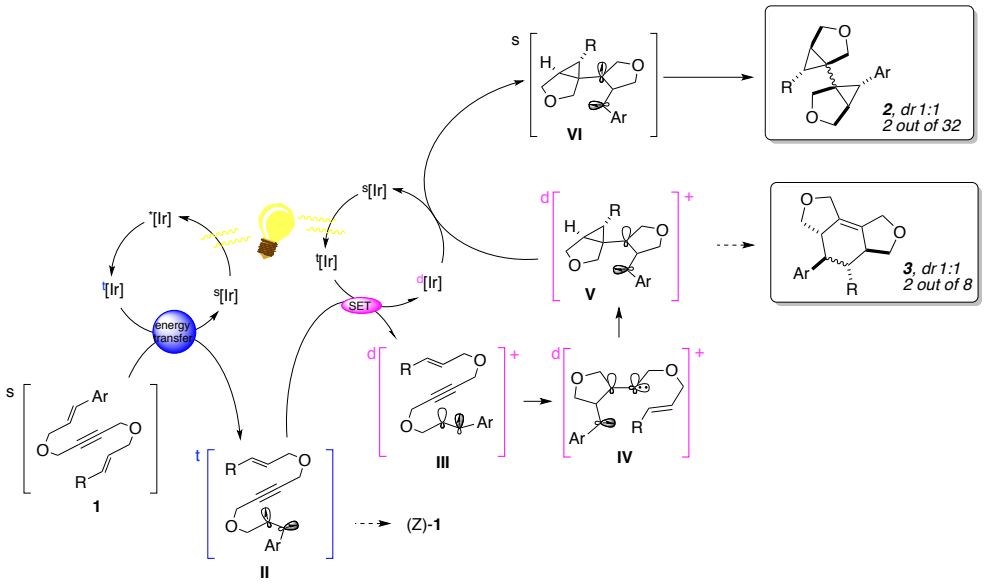
Figure 16: 5 mol % of **PC4**, Yield of Blue line **21a**, Yield of Orange line **22a**, Conversion of **20a**

The mechanism of these domino sequences was then studied in order to solve the riddle on the reactivity responsible for the formation of products. Styryl fragments without strongly donating substituents have oxidation potentials [225] that cannot be accessed with the photocatalysts used in this study. Spin transfer alone could explain formation of (*Z*)-**20a**, *via* racemization of its triplet state prior to relaxation, but falls short in providing a rational for the formation of either **21** or **22**. We thus resorted to DFT modeling to shed light on the outcome of these polycyclizations, which led to the possible pathway presented in Scheme 61.

Optimizations were carried out without constraints at the M06/Def2-svp level, which proved able to reproduce experimental (photo)redox potentials within few kcal/mol of error, [211] starting from model dienyne **20a** (Ar = R = H). Its optimized geometry *in vacuo* was then used as starting point for all of the potential intermediate species, namely the radical cation, the radical anion and the neutral triplet respectively. The wavefunction did not converge modeling the two formers. On the contrary, optimization smoothly led to the expected structure with the two mono-occupied orbitals arranged almost perpendicularly in the case of the triplet **II'**. Surprisingly, removal of one electron from this system enabled the convergence of the wavefunction modeling a radical cation. Even more surprisingly, the optimization led directly to a tricyclic species (**V'**), in which three of the four cycles of **21a** were already established and the spin and charge densities lie mostly on the trivalent benzylic and cyclic carbons, respectively. Efforts to locate any stationary point in between proved fruitless, suggesting a strong energetic convenience for the reaction. Formal one-electron reduction readily delivered the tetracycle **21** upon optimization, terminating the sequence. We then modeled the corresponding species on substrate **20a**, including implicit solvent effects because DMF is especially suited to stabilize cations. Nonetheless, direct oxidation of **1** to **III** by ^{t}**Ir** complex is still unfeasible. This

redox has a positive ΔG of +14.9 kcal/mol. However, triplet **II** lies 47 kcal/mol above its singlet ground state (Ar = Ph, R = H). This is close to literature data for similar reagents, in agreement with their proposed formation by spin-transfer from an excited iridium photocatalyst. Single electron oxidation of **II** lead to radical cation **III**, via single electron transfer (SET) through the involvement of a second excited PC molecule. Although statistically unfavorable as the average concentration in solution of both ^{t}**Ir** and **II** is always tiny, this redox has a large negative calculated ΔG of -32.2 kcal/mol. This is due to the reduced oxidation potential of triplet **II** compared to singlet **1**, somehow paralleling the peculiar redox features of any PC. The geometry of **III** is closer to that of **1** to allow better delocalization of its empty and singly-occupied orbitals, hence locking the initial (*E*)-configuration of the styryl arm. This intermediate can reversibly deliver **IV** (ΔG +4.5 kcal/mol) through a low barrier transition state of +5.2 kcal/mol in ΔG, thus establishing the first cycle of **21**. The divalent carbon atom of the starting alkyne displays a carbenoid character in intermediate **IV**, as witnessed both by population analyses and by its geometry. The angle with its two neighboring carbons sinks indeed to 162° from the initial linear arrangement. This species evolves barrierless to tricyclic radical cation **V** (ΔG -35.3 kcal/mol), in analogy to observations on the first simplified dienyne. Scan of the potential energy surface were essentially flat prior to extensive stabilization as long as the cyclopropanation proceeds. Reduction of **V** can occur regenerating the PC. This redox is thermodynamically favored (ΔG = -79.7 kcal/mol) and should have essentially no barrier as previous SETs, albeit being limited by the very same concentration effects. Alternatively, a chain reaction with a second molecule of **1** cannot be exclude at present stage, as quantum chemical calculations could not take into account concentration effects. Optimization of putative intermediate **VI** led directly to tetracycle **21**, establishing the second cyclopropyl ring. The

involvement of cationic intermediates correlates with the beneficial effect observed experimentally by increasing solvent polarity.

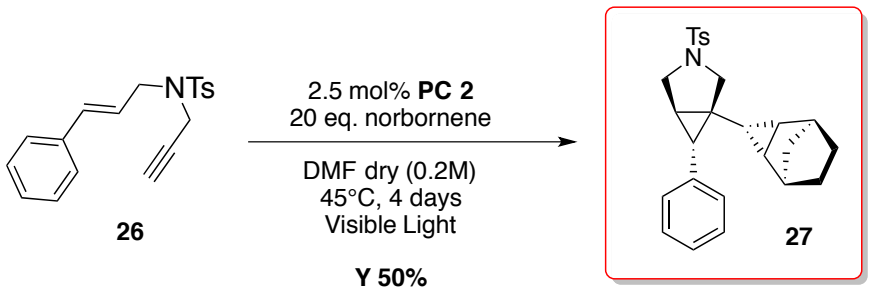


Scheme 58 Energy lowest reaction pathway

The formation of **3** from intermediate **V** can be explained through cyclopropane ring-opening due to the presence of an α-carbocation. The corresponding TS has a barrier of +17.2 kcal/mol, which is sufficiently small to compete with formation of **2** if the reduction of **V** does not take place rapidly. Upon this ring-opening, tricycle **3** eventually forms by SET/intermolecular radical recombination in analogy to **2**. This pathway correlates with the lower yields of **3** using allylated substrates **k-o**, which result from their unstable carbocationic intermediate compared to bis-arylated ones (**a-j**). The near 1:1 dr observed among all products **2** and **3** is consistent with the proposed mechanistic rationale too. It depends on the initial conformation of **1**, in which its two alkene arms can be either on the same or on the opposite face in respect to the central butyn fragment. These conformations are equally probable and the two pathways evenly take place. In

all cases the prochirality of the two olefins is retained in each product, while their relative arrangement is scrambled among the diastereomers of **2** and **3**. Overall, the PC would play two distinct roles in this scenario, acting both as a spin sensitizer towards a styryl fragment and as a monoelectronic redox catalyst on the excited substrate. While both strategies are routinely employed and can even be in competition, we are unwere of previous propositions of their cooperation in a single domino sequence. This dual role, which in turn requires two photons to generate a molecule of product, might correlate with the beneficial effect observed by performing reactions in NMR tubes that have high surface/volume ratios.

We then aimed to trap intermolecularly the carbenoid intermediate observed by DFT to strengthen modeling data. The 1,6-enyne **4** (Scheme 3), which features a terminal alkyne group, was thus reacted under standard conditions in the presence of 20 equiv. of norbornene. To our delight, desired polycycle **5** was isolated in 50% yield as a single diastereomer upon four days of irradiation, together with (*Z*)-**4**. This result is consistent with the intermediate formation is solution of a carbenoid species on the terminal sp carbon of **4**, in analogy to the proposed reaction mechanism.



Scheme 59: Intermolecular carbenoid trapping

8.3 Conclusion

We reported the original behaviour of dienynes in the presence of visible light and an iridium photocatalyst. Reagents can be converted to highly complex tetracyclic frameworks by the ordered rearrangement of their four π-bonds into four new σ-ones. By likely combining a spin-sensitizer and a redox role, the catalyst can trigger formation of a carbenoid reactive intermediate, which can be then efficiently engaged in cyclopropanation reactions.

8.4 Experimental section

Synthesis of dienynes - GP-1: To a solution of but-2-yne-1,4-diol (1 eq.) in THF dry (1 M) was added dropwise $ZnEt_2$ (2 eq., 1 M in hexane). The resulting mixture was stirred until it turned cloudily white (30 min). Aryl allyl acetate (2.05 eq.) and $Pd(PPh_3)_4$ (0.1 eq.) were then added. The reaction was stirred until complete conversion, monitored by TLC. The mixture was then concentrated and carefully purified by flash chromatography.

Synthesis of asymmetric dienynes - GP-2: To a solution of enynol (1 eq.) in dry THF/DMF (0.6 M, 4:1) at 0°C was added NaH (1.5 eq., 60 % wt in paraffin oil). The resulting mixture was stirred half an hour. Then alkyl halide (1.1 eq.) was added. The mixture was kept at room temperature and stirred overnight. The mixture was then concentrated and carefully purified by flash chromatography.

Photocatalytic reactions - GP-3: Under argon a solution of desiderate substrate (0.2 mmol, 1 eq.) in dry and degassed DMF (0.2 M, 1 mL) was added into a NMR tube charged with $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (5.5 mg, 0.005 mmol, 2.5 mol%). The reaction was irradiated at 45 °C for 24 hours. The mixture was then concentrated and carefully purified by preparative TLC chromatography.

Photocatalytic reactions - GP-4: Under argon a solution of desiderate substrate (0.2 mmol, 1 eq.) in dry and degassed DMF (0.2 M, 1 mL) was added into a NMR tube charged with $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (5.5 mg, 0.005 mmol, 2.5 mol%). The reaction was irradiated at 45 °C for 48 hours. The mixture was then concentrated and carefully purified by preparative TLC chromatography.

1,4-bis(((*E*)-3-(*o*-tolyl)allyl)oxy)but-2-yne (20b): The **GP-1** was followed using (E)-3-(o-tolyl)allyl acetate (1 g, 5.26 mmol, 2.1 eq.). Purification by chromatography on silica gel yielded **21b** (307 g, 34 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.6 (Cq), 135.5 (Cq), 131.1 (CH), 130.2 (CH), 127.6 (CH), 126.4 (CH), 126.1 (CH), 125.7 (CH), 82.4 (Cq), 70.5 (CH_2), 57.3 (CH_2), 19.8 (CH_3). **ESI-MS** calcd for $C_{24}H_{26}NaO_2$ $[M+Na]^+$ 369.18, found 369.40

1,4-bis(((*E*)-3-(3-fluoro-4-methylphenyl)allyl)oxy)but-2-yne (20d): The **GP-1** was followed using (*E*)-3-(3-fluoro-4-methylphenyl)allyl acetate (1 g, 4.09 mmol, 2.1 eq.). Purification by chromatography on silica gel yielded **20d** (222 g, 25 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.38 (d, *J* = 244.3 Hz, Cq), 136.23 (d, *J* = 7.7 Hz, CH, Cq), 131.99 (d, *J* = 2.5 Hz, CH), 131.40 (d, *J* = 5.5 Hz, CH), 125.42 (CH), 124.29 (d, *J* = 17.6 Hz, Cq), 122.07 (d, *J* = 3.2 Hz, CH), 112.51 (d, *J* = 22.8 Hz, CH), 82.42 (Cq), 70.06 (CH_2), 57.45 (CH_2), 14.33 (d, *J* = 3.4 Hz, CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.7. **ESI-MS** calcd for $C_{24}H_{24}F_{26}NaO_2$ $[M+Na]^+$ 405.16, found 405.32

1,4-bis(((*E*)-3-(4-(trifluoromethyl)phenyl)allyl)oxy)but-2-yne (20e): The **GP-1** was followed using (*E*)-3-(4-(trifluoromethyl)phenyl)allyl acetate (1 g, 4.09 mmol, 2.1 eq.). Purification by chromatography on silica gel yielded **20e** (223 g, 25 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 4H), 7.47 (d, *J* = 8.1 Hz, 4H), 6.68 (d, *J* = 16.0 Hz, 2H), 6.38 (dt, *J* = 16.0, 5.8 Hz, 2H), 4.29 (s, 4H), 4.27 – 4.25 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.0 (Cq), 131.3 (CH), 129.5 (q, *J* = 32.3 Hz, Cq), 128.0 (CH), 126.6 (CH), 125.5 (q,

J = 3.8 Hz, CH), 124.1 (q, *J* = 271.8 Hz, CF_3), 82.4 (Cq), 69.9 (CH_2), 57.7 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.5. **ESI-MS** calcd for $C_{24}H_{20}F_6KO_2$ $[M+K]^+$ 493.10, found 493.37

1,4-bis(((*E*)-3-(3-(trifluoromethyl)phenyl)allyl)oxy)but-2-yne (20f): The **GP-1** was followed using (*E*)-3-(3-(trifluoromethyl)phenyl)allyl acetate (1 g, 4.09 mmol, 2.1 eq.). Purification by chromatography on silica gel yielded **20f** (222 mg, 25 %) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) 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). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.3 (Cq), 131.4 (CH), 131.0 (q, J = 32.2 Hz, Cq), 129.6 (CH), 129.0 (CH), 127.3 (CH), 124.2 (d, *J* = 3.9 Hz, CH), 124.0 (q, *J* = 272.3 Hz, Cq), 123.1 (q, *J* = 3.8 Hz, CH), 82.4 (Cq), 69.9 (CH_2), 57.7 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.8. **ESI-MS** calcd for $C_{24}H_{20}F_6NaO_2$ $[M+Na]^+$ 477.13, found 477.34

1,4-bis(((*E*)-3-(naphthalen-2-yl)allyl)oxy)but-2-yne (20g): The **GP-2** was followed using (*E*)-3-(naphthalen-2-yl)allyl acetate (1 g, 4.4 mmol, 2.1 eq.). Purification by chromatography on silica gel yielded **20g** (127 mg, 15 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 – 7.69 (m, 8H), 7.62 – 7.59 (m, 2H), 7.46 – 7.43 (m, 4H), 6.81 (d, *J* = 15.8 Hz, 2H), 6.42 (dt, *J* = 15.9, 6.1 Hz, 2H), 4.31 (brs, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.0 (Cq), 133.5 (Cq) 133.4 (Cq), 133.1 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 126.6 (CH), 126.3 (CH), 126.0 (CH), 125.5 (CH), 123.5 (CH), 82.5 (Cq), 70.4 (CH_2), 57.5 (CH_2). **ESI-MS** calcd for [M+Na]+ 441.18, found 441.20

***N*-cinnamyl-*N*-(4-((*N*-cinnamyl-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide (20i)**: To a solution of *N*-cinnamyl-4-methylbenzenesulfonamide (490 mg, 2.1 eq.) and K_2CO_3 (340 mg, 3 eq.) in dry

CH_3CN (1.5 mL, 0.5 M) was added 1,4-dichloro-butyne (100 mg ,1 eq.). The mixture was reflux 48 hours. The reaction was cooled to room temperature and diluted with ethyl acetate. The organic layers were extracted, washed with brine, dried over sodium sulfate, filtrated and concentrated. The crude was purified by chromatography column yielding **20i** as a white solid (300 mg, 60%). Eluent: hexane:ethylacetate (8:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 4H), 7.33 – 7.25 (m, 14H), 6.41 (d, *J* = 15.8 Hz, 2H), 5.98 (dt, *J* = 15.8, 6.8 Hz, 2H), 3.90 (s, 4H), 3.82 (dd, *J* = 6.8, 1.3 Hz, 4H), 2.36 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.8 (Cq), 136.1 (Cq), 135.9 (Cq), 134.7 (CH), 129.6 (CH_2), 128.7 (CH_2), 128.2 (CH), 127.6 (CH_2), 126.5 (CH_2), 122.7 (CH), 78.5 (Cq), 48.6 (CH_2), 35.9 (CH_2), 21.5 (CH_3). **ESI-MS** calcd for [M+Na]+ 647.20, found 647.25

(*E*)-(3-((4-(allyloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)benzene (23a): The **GP-2** was followed using 4-(cinnamyloxy)but-2-yn-1-ol (350 mg, 1.7 mmol, 1 eq.). Purification by chromatography on silica gel yielded **23a** (251 mg, 61 %) as a transparent oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 6.85 (m, 5H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.92 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.35 – 5.21 (m, 2H), 4.26 – 4.22 (m, 6H), 4.08 (dt, *J* = 5.7, 1.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.5 (Cq), 133.9 (CH), 133.2 (2CH), 128.5 (2CH), 127.8 (CH), 126.5 (CH2), 125.1 (CH), 117.8 (CH), 82.4 (Cq), 82.3 (Cq), 70.6 (CH_2), 70.2 (CH_2), 57.4 (CH_2), 57.3 (CH_2). **ESI-MS** calcd for $C_{16}H_{18}KO_2$ [M+K]+ 281.09, found 281.23

(*E*)-1-(3-((4-(allyloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)-2-methylbenzene (23b): The **GP-2** was followed using (*E*)-4-((3-(*o*-tolyl)allyl)oxy)but-2-yn-1-ol (500 mg, 2.3 mmol, 1 eq.). Purification by chromatography on silica gel yielded **23b** (423 mg, 71 %) as a transparent oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 –

7.44 (m, 1H), 7.19 – 7.16 (m, 3H), 6.87 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.8, 6.2 Hz, 1H), 5.93 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.36 – 5.21 (m, 2H), 4.27 – 4.21 (m, 6H), 4.10 – 4.08 (m, 2H), 2.36 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.6 (Cq), 135.4 (Cq), 133.9 (CH), 131.1 (CH), 130.2 (CH), 127.6 (CH), 126.4 (CH), 126.0 (CH), 125.7 (CH), 117.7 (CH), 82.4 (Cq), 82.3 (Cq), 70.5 (CH_2), 70.4 (CH_2), 57.3 (CH_2), 57.2 (CH_2), 19.7 (CH_3). **ESI-MS** calcd for $C_{17}H_{20}KO_2$ [M+K]+ 295.11, found 295.27

(*E*)-4-(3-((4-(allyloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)-2-fluoro-1-methylbenzene (23c): The **GP-2** was followed using (*E*)-4-((3-(3-fluoro-4-methylphenyl)allyl)oxy)but-2-yn-1-ol (390 mg, 1.6 mmol, 1 eq.). Purification by chromatography on silica gel yielded **23c** (404 mg, 89 %) as a transparent oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.13 – 7.02 (m, 3H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.0 Hz, 1H), 5.91 (ddt, *J* = 17.4, 10.4, 5.7 Hz, 1H), 5.35 – 5.20 (m, 2H), 4.24 – 4.20 (m, 6H), 4.08 – 4.06 (m, 2H), 2.25 (3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 161.4 (d, *J* = 244.3 Hz, Cq), 136.3 (d, *J* = 8.0 Hz, Cq), 133.9 (CH), 132.0 – 131.9 (m, CH), 131.4 (d, *J* = 5.6 Hz, CH), 125.5 (CH_2), 124.3 (d, *J* = 17.9 Hz, Cq), 122.07 (d, *J* = 3.2 Hz, CH), 117.8 (d, *J* = 3.7 Hz, CH), 112.5 (d, *J* = 22.8 Hz, CH), 82.5 (Cq), 82.2 (Cq), 70.6 (CH_2), 70.0 (CH_2), 57.4 (CH_2), 57.4 (CH_2), 14.32 (d, *J* = 3.5 Hz, CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.8. **ESI-MS** calcd for $C_{17}H_{19}FO_2$ [M+K]+ 313.10, found 313.22

(*E*)-1-(3-((4-(allyloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)-3-(trifluoromethyl)benzene (23d): The **GP-2** was followed using (*E*)-4-((3-(3-(trifluoromethyl)phenyl)allyl)oxy)but-2-yn-1-ol (300 mg, 1.1 mmol, 1 eq.). Purification by chromatography on silica gel yielded **23d** (128 mg, 37 %) as a transparent oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 – 7.40 (m, 4H), 6.67 (d, *J* = 16.0 Hz, 1H), 6.36 (dt, *J* = 16.0, 5.9 Hz, 1H), 5.91 (ddt, *J* = 17.3, 10.3, 5.7 Hz,

1H), 5.35 – 5.20 (m, 2H), 4.27 – 4.21 (m, 6H), 4.07 (dt, *J* = 5.7, 1.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.3 (Cq), 135.6 (d, *J* = 3.6 Hz, CH), 133.9 (CH), 131.4 (CH), 130.6 (d, *J* = 32.4 Hz, Cq), 129.6 (CH), 129.0 (CH), 127.3 (CH), 124.3 (q, *J* = 3.6 Hz, CH), 124.0 (q, *J* = 264.9 Hz, CF_3), 123.1 (q, *J* = 3.8 Hz, CH), 117.9 (CH), 82.6 (Cq), 82.1 (Cq), 70.7 (CH_2), 69.8 (CH_2), 57.6 (CH_2), 57.4 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.8. **ESI-MS** calcd for $C_{17}H_{11}F_3O_2$ [M+K]+ 349.08, found 349.20

(*E*)-(3-(oct-7-en-2-yn-1-yloxy)prop-1-en-1-yl)benzene (23e): To a stirred solution of the (E)-(3-(prop-2-yn-1-yloxy)prop-1-en-1-yl)benzene (500 mg, 2.9 mmol, 1.15 eq.) in THF (10 mL, 0.25 M) was added *n*-Butyllithium (1.6 M in hexane, 1.7 mL, 2.7 mmol, 1.1 eq.) at -78 °C. After stirring for 1 hour at -78 °C, 5-bromo-1-pentene (300 μL, 2.5 mmol, 1 eq.) was slowly added followed by DMSO (6.9 mL, 35 eq.) the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched by addition of saturated NH_4Cl solution, extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by chromatography column yielding **23e** as a colourless oil (176 mg, 300%). Eluent: hexane:ethylacetate (8:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 5H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.32 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.82 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.10 – 5.00 (m, 2H), 4.25 (dd, *J* = 6.2, 1.4 Hz, 2H), 4.21 (t, *J* = 2.2 Hz, 2H), 2.28 (tt, *J* = 7.1, 2.2 Hz, 2H), 2.22 – 2.17 (m, 2H), 1.66 (p, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.8 (CH), 136.6 (Cq), 133.0 (CH), 128.5 (2CH), 127.7 (CH), 126.5 (2CH), 125.5 (CH), 115.2 (CH_2), 86.8 (Cq), 76.1 (Cq), 70.0 (CH_2), 57.7 (CH_2), 32.8 (CH_2), 27.8 (CH_2), 18.2 (CH_2). **ESI-MS** calcd for $C_{17}H_{20}NaO$ $[M+Na]^+$ 263.14, found 263.15

***N*-allyl-*N*-(4-(cinnamyloxy)but-2-yn-1-yl)-4-methylbenzenesulfonamide (23f):** was obtained following a literature procedure using *N*-allyl-4-methylbenzenesulfonamide (250 mg, 1.2 mmol, 1 eq.) and (*E*)-(3-((4-bromobut-2-yn-1-yl)oxy)prop-1-en-1-yl)benzene (350 mg, 1.32 mmol, 1.1 eq.). Purification by chromatography on silica gel yielded **23f** (309 mg, 65 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.76 (m, 2H), 7.41 – 7.26 (m, 7H), 6.59 (d, *J* = 15.9 Hz, 1H), 6.22 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.82 – 5.71 (m, 1H), 5.34 – 5.25 (m, 2H), 4.17 (s, 2H), 4.05 (dd, *J* = 6.1, 1.4 Hz, 2H), 3.97 (s, 2H), 3.85 (d, *J* = 6.4 Hz, 2H), 2.40 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5 (Cq), 136.4 (Cq), 136.1 (Cq), 133.3 (CH), 132.0 (CH), 129.4 (2CH), 128.6 (2CH), 127.9 (CH), 127.8 (2CH), 126.5 (2CH), 124.9 (CH), 119.8 (CH), 81.5 (Cq), 79.2 (Cq), 70.0 (CH_2), 57.0 (CH_2), 49.1 (CH_2), 36.1 (CH_2), 21.5 (CH_3). **ESI-MS** calcd for $C_{23}H_{25}NNaO_3S$ [M+Na]+ 418.14, found 418.22

(*E*)-(3-((4-((3-methylbut-2-en-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)benzene (23g): The **GP-2** was followed using 4-(cinnamyloxy)but-2-yn-1-ol (350 mg, 1.7 mmol, 1 eq.). Purification by chromatography on silica gel yielded **23g** (334 mg, 73 %) as a transparent oil. **^{1}H NMR** (400 MHz, CDCl3) δ 7.40 – 7.38 (m, 2H), 7.34 – 7.30 (m, 2H), 7.27 – 7.23 (m, 1H), 6.64 (d, *J* = 16.0 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.35 (dddd, *J* = 7.1, 5.6, 2.9, 1.4 Hz, 1H), 4.35 – 4.14 (m, 6H), 4.06 (d, *J* = 7.0 Hz, 2H), 1.76 (s, 3H), 1.71 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.2 (Cq), 136.5 (Cq), 133.2 (CH), 128.5 (2CH), 127.8 (CH), 126.5 (2CH), 125.1 (CH), 120.2(CH), 82.8 (Cq), 82.0 (Cq), 70.2 (CH_2), 66.0 (CH_2), 57.4 (CH_2), 57.1 (CH_2), 25.8 (CH_3), 18.0 (CH_3). **ESI-MS** calcd for $C_{18}H_{22}KO_2$ [M+K]+ 309.13, found 309.30

(*E*)-(3-((4-(cyclohex-2-en-1-yloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)benzene (23h): The **GP-2** was followed using 4-(cinnamyloxy)but-2-yn-1-ol (300 mg, 1.5

mmol, 1 eq.). Purification by chromatography on silica gel yielded **23h** (209 mg, 50 %) as a transparent oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 5H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.91 – 5.77 (m, 2H), 4.27 – 4.22 (m, 6H), 4.09 (brs, 1H), 2.08 – 1.94 (m, 2H), 1.87 – 1.68 (m, 3H), 1.61 – 1.54 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.5 (Cq), 133.2 (CH), 131.4 (CH), 128.5 (2CH), 127.7 (CH), 127.1 (CH), 126.5(2CH), 125.2 (CH), 83.1 (Cq), 81.7 (Cq), 71.7 (CH_2), 70.2 (CH_2), 57.4 (CH_2), 55.5 (CH_2), 28.0 (CH_2), 25.1 (CH_2), 19.0 (CH_2). **ESI-MS** calcd for $C_{19}H_{22}KO_2$ $[M+K]^+$ 321.13, found 321.27

(*E*)-1-(3-((4-(cyclohex-2-en-1-yloxy)but-2-yn-1-yl)oxy)prop-1-en-1-yl)-3-(trifluoromethyl)benzene (23i): The **GP-2** was followed using (*E*)-4-((3-(3-(trifluoromethyl)phenyl)allyl)oxy)but-2-yn-1-ol (300 mg, 1.1 mmol, 1 eq.). Purification by chromatography on silica gel yielded **23i** (175 mg, 45 %) as a transparent oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.56 – 7.41 (m, 3H), 6.67 (d, *J* = 16.0 Hz, 1H), 6.35 (dt, *J* = 16.1, 5.9 Hz, 1H), 5.90 – 5.77 (m, 2H), 4.26 (s, 6H), 4.07 (brs, 1H), 2.08 – 1.93 (m, 2H), 1.87 – 1.64 (m, 3H), 1.57 – 1.52 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.4 (Cq), 131.5 (CH), 131.3 (CH), 131.0 (d, *J* = 32.1 Hz, Cq), 129.6 (CH), 129.0 (CH), 127.4 (CH), 127.0 (CH), 124.25 (q, *J* = 3.7 Hz, CH), 124.05 (q, *J* = 272.4 Hz, CF_3), 123.17 (q, *J* = 3.7 Hz, CH), 83.4 (Cq), 81.5 (Cq), 71.8 (CH), 69.8 (CH_2), 57.7 (CH_2), 55.5 (CH_2), 28.0 (CH_2), 25.1 (CH_2), 19.0 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.8. **ESI-MS** calcd for $C_{20}H_{21}F_3KO_2$ $[M+K]^+$ 389.11, found 389.23

(*E*)-(3-((5-(allyloxy)-2-methylpent-3-yn-2-yl)oxy)prop-1-en-1-yl)benzene (23j): To a stirred solution of the (*E*)-(3-((2-methylbut-3-yn-2-yl)oxy)prop-1-en-1-yl)benzene (500 mg, 2.5 mmol, 1 eq.) in dry THF (10 mL, 0.25 M) was added *n*-Butyllithium (1.6 M in hexane, 1.7 mL, 2.75 mmol, 1.1 eq.) at -78 °C. After

stirring for 1 hour at -78 °C, paraformaldehyde (113 mg, 3.75 mmol, 1.5 eq.) was slowly added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched by addition of saturated NH_4Cl solution, extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel to give 4-(cinnamyloxy)-4-methylpent-2-yn-1-ol (80 %, 460 mg). The **GP-2** was followed using 4-(cinnamyloxy)-4-methylpent-2-yn-1-ol (300 mg, 1.1 mmol, 1 eq.). Purification by chromatography on silica gel yielding **23j** (300 mg, 45 % overall yield) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.32 (dt, *J* = 15.9, 6.0 Hz, 1H), 5.97 – 5.87 (m, 1H), 5.34 – 5.21 (m, 2H), 4.28 (d, *J* = 6.0 Hz, 2H), 4.21 (s, 2H), 4.07 (d, *J* = 5.8 Hz, 2H), 1.53 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.9 (Cq), 134.0 (CH), 131.7 (CH), 128.4 (2CH), 127.5 (CH), 126.7 (CH), 126.4 (2CH), 117.9 (CH_2), 88.5 (Cq), 80.1 (Cq), 70.5 (CH_2), 70.4 (Cq), 65.2 (CH_2), 57.4 (CH_2), 28.9 ($2CH_3$). **ESI-MS** calcd for $C_{18}H_{22}KO_2$ $[M+K]^+$ 309.13, found 309.20

(1*S*,1'*S*,5*R*,5'*R*,6*S*,6'*S*)-6,6'-diphenyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21a was isolated was isolated with 25% (white solid, 16 mg, 0.05 mmol) following the **GP-3** using **20a** (64 mg, 0.2 mmol) as reagent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 4H), 7.23 – 7.17 (m, 6H), 3.79 (d, *J* = 8.0 Hz, 2H), 3.59 (dd, *J* = 11.4, 8.0 Hz, 4H), 2.78 – 2.74 (m, 2H), 2.03 (d, *J* = 4.7 Hz, 2H), 1.79 (dd, *J* = 4.7, 2.8 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 136.6 (Cq), 129.1 (2CH), 128.2 (2CH), 126.2 (CH), 72.9 (CH_2), 69.1 (CH_2), 33.9 (Cq), 28.7 (CH), 27.1 (CH). **HRMS** calcd for $C_{22}H_{23}O_2$ $[M+H]^+$ 319.1693, found 319.1695.

(1*S*,5*R*,6*S*,6'*R*)-6,6'-diphenyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21a' was isolated was isolated with 25% (white solid, 16 mg, 0.05 mmol) following the **GP-3** using **20a** (64 mg, 0.2 mmol) as reagent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 6H), 7.06 – 7.03 (m, 4H), 3.83 (d, *J* = 8.3 Hz, 2H), 3.70 (dd, *J* = 8.3, 2.8 Hz, 2H), 3.54 (q, *J* = 8.6 Hz, 2H), 1.98 (d, *J* = 4.7 Hz, 2H), 1.63 (dd, *J* = 4.7, 2.8 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.9 (Cq), 128.1 (2CH), 127.7 (2CH), 126.2 (CH), 74.1 (CH_2), 70.0 (CH_2), 33.9 (Cq), 30.3 (CH), 27.4 (CH). **HRMS** calcd for $C_{22}H_{23}O_2$ $[M+H]^+$ 319.1693, found 319.1697.

(3a*S*,4*R*,5*R*,5a*S*)-4,5-diphenyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22a was isolated was isolated with 16% (white solid, 10.1 mg, 0.03 mmol) following the **GP-3** using **20a** (64 mg, 0.2 mmol) as reagent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 6.79 (m, 10H), 4.48 – 4.44 (m, 2H), 4.29 (d, *J* = 11.4Hz, 2H),3.84 (t, *J* = 7.3 Hz, 2H), 3.38 (dd, *J* = 11.0, 7.8 Hz, 2H), 3.19 – 3.05 (m, 2H), 3.05 – 2.88 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.5 (Cq), 129.5 (Cq), 128.3 (2CH), 127.5 (2CH), 126.3 (CH), 72.9 (CH_2), 67.8 (CH_2), 50.4 (CH), 49.2 (CH). **HRMS** calcd for $C_{22}H_{22}NaO_2$ $[M+Na]^+$ 341.1512, found 341.1511.

(3a*R*,4*S*,5*R*,5a*S*)-4,5-diphenyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22a' was isolated was isolated with 16% (white solid, 10 mg, 0.03 mmol) following the **GP-3** using **20a** (64 mg, 0.2 mmol) as reagent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.14 – 7.08 (m, 6H), 6.67 – 6.64 (m, 4H), 4.47 – 4.36 (m, 4H), 4.14 (t, *J* = 7.8 Hz, 2H), 3.32 (dd, *J* = 10.4, 7.8 Hz, 2H), 3.16 (brs, 2H), 2.84 (d, *J* = 1.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.3 (Cq), 132.0 (Cq), 128.8 (2CH), 127.8 (2CH), 126.4 (CH), 72.1 (CH_2), 68.3 (CH_2), 47.3 (CH), 42.6 (CH). **HRMS** calcd for $C_{22}H_{22}NaO_2$ $[M+Na]^+$ 341.1512, found 341.1515.

(1*S*,1'*S*,5*R*,5'*R*,6*S*,6'*S*)-6,6'-di-*o*-tolyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21b was isolated was isolated with 37% (white solid, 24.2 mg, 0.07 mmol) following the **GP-3** using **20b** (69 mg, 0.2 mmol) as reagent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.12 (m, 6H), 7.09 – 7.07 (m, 2H), 3.81 (d, *J* = 7.9 Hz, 2H), 3.57 (d, *J* = 7.9 Hz, 2H), 3.28 (d, *J* = 7.9 Hz, 2H), 2.68 (dd, *J* = 7.9, 2.9 Hz, 2H), 2.40 (s, 6H), 2.03 (dd, *J* = 5.0, 2.8 Hz, 2H), 1.94 (d, *J* = 4.9 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.9 (Cq), 134.7 (Cq), 130.3 (CH), 126.8 (CH), 126.1 (CH), 125.4 (CH), 72.5 (CH_2), 68.9 (CH_2), 34.0 (Cq), 28.9 (CH_3), 25.0 (CH), 20.2 (CH). **HRMS** calcd for $C_{24}H_{26}NaO_2$ $[M+Na]^+$ 369.1825, found 3691828.

(1*R*,1'*S*,5*S*,5'*R*,6*R*,6'*S*)-6,6'-di-*o*-tolyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21b' was isolated was isolated with 26 % (white solid, 17.0 mg, 0.05 mmol) following the **GP-3** using **20b** (69 mg, 0.2 mmol) as reagent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.22 – 7.10 (m, 6H), 6.66 – 6.63 (m, 2H), 3.79 (d, *J* = 8.2 Hz, 2H), 3.67 (dd, *J* = 8.3, 2.8 Hz, 2H), 3.61 (d, *J* = 8.5 Hz, 2H), 3.54 (d, *J* = 8.5 Hz, 2H), 2.34 (s, 6H), 2.00 (d, *J* = 5.0 Hz, 2H), 1.75 (dd, *J* = 5.0, 2.8 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.4 (Cq), 135.6 (Cq), 130.2 (CH), 126.1 (CH), 125.7 (CH), 125.5 (CH), 73.8 (CH_2), 70.0 (CH_2), 34.2 (Cq), 26.9 (CH), 26.8 (CH_3), 20.3 (CH). **HRMS** calcd for $C_{24}H_{26}NaO_2$ $[M+Na]^+$ 369.1825, found 3691822.

(3a*S*,4*R*,5*R*,5a*S*)-4,5-di-*o*-tolyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22b was isolated was isolated with 28 % (white solid, 19.4 mg, 0.06 mmol) following the **GP-3** using **20b** (69 mg, 0.2 mmol) as reagent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 2H), 7.04 – 7.01 (m, 2H), 6.89 (d, *J* = 4.4 Hz, 4H), 4.46 (d, *J* = 13.0 Hz, 2H), 4.29 (d, *J* = 11.7 Hz, 2H), 3.83 (t, *J* = 7.2 Hz, 2H), 3.54 – 3.21 (m, 4H), 3.12 – 3.07 (brs, 2H), 2.23 (s, 6H). **^{13}C NMR** (75 MHz,

$CDCl_3$) δ 140.5 (Cq), 135.1 (Cq), 130.0 (Cq), 129.7 (CH), 125.9 (CH), 125.9 (CH), 125.4 (CH), 72.4 (CH_2), 67.7 (CH_2), 51.8 (CH), 43.2 (CH), 20.1 (CH_3). **HRMS** calcd for $C_{24}H_{26}KO_2$ $[M+K]^+$ 385.1564, found 385.1564.

(3a*R*,4*S*,5*R*,5a*S*)-4,5-di-*o*-tolyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22b' was isolated was isolated with 10 % (white solid, 7 mg, 0.02 mmol) following the **GP-3** using **20b** (69 mg, 0.2 mmol) as reagent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.07 – 7.03 (m, 2H), 7.00 – 6.94 (m, 4H), 6.62 (dd, *J* = 7.6, 1.4 Hz, 2H), 4.43 (q, *J* = 12.4, 11.3 Hz, 4H), 4.10 (t, *J* = 7.5 Hz, 2H), 3.29 – 3.25 (m, 2H), 3.19 (brs, 2H), 3.13 – 3.12 (m, 2H), 1.82 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.5 (Cq), 136.7 (Cq), 132.4 (Cq), 129.8 (CH), 128.0 (CH), 126.3 (CH), 125.7 (CH), 72.2 (CH_2), 68.4 (CH_2), 43.5 (CH), 40.2 (CH), 18.9 (CH_3). **HRMS** calcd for $C_{24}H_{26}KO_2$ $[M+K]^+$ 385.1564, found 385.1564.

(1*R*,1'*R*,5*R*,5'*R*,6*R*,6'*R*)-6,6'-di(thiophen-2-yl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21c was isolated was isolated with 19 % (yellow pale oil, 12.5 mg, 0.04 mmol) following the **GP-3** using **20c** (66 mg, 0.2 mmol) as reagent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 5.1 Hz, 2H), 6.96 – 6.94 (m, 2H), 6.81 (d, *J* = 3.4 Hz, 2H), 3.99 – 3.89 (m, 2H), 3.83 – 3.74 (m, 4H), 3.70 – 3.63 (m, 2H), 2.16 (d, *J* = 4.2 Hz, 2H), 1.83 (dd, *J* = 4.4, 2.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.6 (Cq), 126.9 (CH), 126.0 (CH), 123.6 (CH), 72.4 (CH_2), 69.2 (CH_2), 34.4 (Cq), 31.6 (CH), 21.8 (CH). **HRMS** cald for $C_{18}H_{18}KO_2S_2$ $[M+K]^+$ 369.0380, found 369.0381.

(1*R*,1'*S*,5*R*,5'*S*,6*R*,6'*S*)-6,6'-di(thiophen-2-yl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21c' was isolated with 18% (pale yellow oil, 12 mg, 0.04 mmol) following the **GP-3** using **20c** (66 mg, 0.2 mmol) as reagent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 5.1, 1.2 Hz, 2H), 6.97 (dd, *J* = 5.2, 3.5

Hz, 2H), 6.80 (d, *J* = 3.6 Hz, 2H), 3.86 (d, *J* = 8.3 Hz, 2H), 3.66 (dd, *J* = 8.4, 2.8 Hz, 2H), 3.62 – 3.56 (m, 4H), 2.26 (d, *J* = 4.6 Hz, 2H), 1.64 (dd, *J* = 4.6, 2.7 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.0 (Cq), 127.1 (CH), 124.6 (CH), 123.2 (CH), 73.7 (CH_2), 70.0 (CH_2), 34.5 (Cq), 29.5 (CH), 25.5 (CH). **HRMS** cald for $C_{18}H_{18}KO_2S_2$ $[M+K]^+$ 369.0380, found 369.0381.

(3a*S*,4*S*,5*S*,5a*S*)-4,5-di(thiophen-2-yl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22c and **(3a*R*,4*R*,5*S*,5a*S*)-4,5-di(thiophen-2-yl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22c'** were isolated with 30 % yield (pale yellow oil, 19.8 mg, 0.06 mmol) following the **GP-3** using **20c** (66 mg, 0.2 mmol) as reagent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 – 7.12 (m, 1H), 7.09 – 7.05 (m, 3H), 6.99 – 6.90 (m, 1H), 6.87 – 6.78 (m, 2H), 6.75 – 6.69 (m, 2H), 6.60 (dd, *J* = 9.9, 3.3 Hz, 1H), 6.53 (dd, *J* = 27.0, 3.1 Hz, 2H), 4.47 (q, *J* = 12.8, 9.3 Hz, 2H), 4.39 – 4.37 (m, 2H), 4.33 – 4.11 (m, 6H), 4.05 – 3.82 (m, 6H), 3.38 – 3.29 (m, 4H), 3.27 – 3.10 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.5 (Cq), 144.4 (Cq), 131.1 (Cq), 129.2 (Cq), 126.4 (2CH), 125.3 (CH), 124.8 (CH), 123.9 (CH), 123.4 (CH), 72.8 (CH_2), 72.1 (CH_2), 68.3 (CH_2), 67.8, (CH_2) 50.7 (CH), 46.8 (CH), 44.1 (CH), 42.9 (CH). **HRMS** cald for $C_{18}H_{18}NaO_2S_2$ $[M+Na]^+$ 353.0640, found 353.0641.

(1*S*,1'*S*,5*R*,5'*R*,6*S*,6'*S*)-6,6'-bis(3-fluoro-4-methylphenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21d was isolated with 20 % yield (white solid, 15.6 mg, 0.04 mmol) following **GP-3** using **20d** (76.5 mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.09 (t, *J* = 8.0 Hz, 2H), 6.82 (dd, *J* = 21.8, 10.2 Hz, 4H), 3.78 (d, *J* = 8.1 Hz, 2H), 3.67 (d, *J* = 8.1 Hz, 2H), 3.53 (d, *J* = 8.1 Hz, 2H), 2.92 (brs, 2H), 2.25 (d, *J* = 1.9 Hz, 6H), 1.97 (d, *J* = 4.6 Hz, 2H), 1.77 (dd, *J* = 4.6, 2.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2 (d, *J* = 244.5 Hz, Cq), 136.5 (d, *J* = 7.5 Hz, CH), 131.0 (d, *J* = 5.8 Hz, CH), 124.3 (CH), 122.5 (d, *J* =

17.2 Hz, CH), 115.3 (d, *J* = 22.4 Hz, CH), 73.0 (CH_2), 69.2 (CH_2), 34.0 (Cq), 29.3 (CH), 26.8 (CH), 14.1 (d, *J* = 3.3 Hz, CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.8. **HRMS** calcd for $C_{24}H_{24}F_2NaO$ $[M+Na]^+$ 405.1637, found 405.1639.

(1*S*,5*R*,6*S*,6'*R*)-6,6'-bis(3-fluoro-4-methylphenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21d' was isolated with 19 % yield (white solid, 14.5 mg, 0.04 mmol) following **GP-3** using **20d** (76.5 mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 7.06 (m, 2H), 6.78 (dd, *J* = 7.8, 1.8 Hz, 2H), 6.68 (dd, *J* = 11.1, 1.8 Hz, 2H), 3.87 (d, *J* = 8.4 Hz, 2H), 3.73 (dd, *J* = 8.4, 2.8 Hz, 2H), 3.65 – 3.44 (m, 4H), 2.29 (d, *J* = 1.9 Hz, 6H), 1.97 (d, *J* = 4.7 Hz, 2H), 1.68 – 1.53 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2 (d, *J* = 244.6 Hz, Cq), 137.6 (d, *J* = 7.4 Hz, CH), 131.1 (CH), 123.4 (d, *J* = 3.2 Hz, CH), 122.6 (d, *J* = 17.2 Hz, CH), 114.0 (d, *J* = 23.0 Hz, CH), 74.0 (CH_2), 70.0 (CH_2), 34.0 (Cq), 29.8 (d, *J* = 1.9 Hz, CH), 27.6 (CH), 14.2 (d, *J* = 3.3 Hz, CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.8. **HRMS** calcd for $C_{24}H_{24}F_2NaO$ $[M+Na]^+$ 405.1637, found 405.1635.

(3a*S*,4*R*,5*R*,5a*S*)-4,5-bis(3-fluoro-4-methylphenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22d was isolated with 15 % yield (white solid, 11.1 mg, 0.03 mmol) following **GP-3** using **20d** (76.5 mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.94 – 6.90 (m, 2H), 6.68 – 6.64 (m, 4H), 4.44 (dd, *J* = 11.1, 2.0 Hz, 2H), 4.31 – 4.22 (m, 2H), 3.83 (t, *J* = 7.4 Hz, 2H), 3.35 (dd, *J* = 10.9, 7.8 Hz, 2H), 3.02 – 2.99 (m, 2H), 2.87 – 2.85 (m, 2H), 2.12 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2 (d, *J* = 244.6 Hz, Cq), 141.2 (d, *J* = 7.0 Hz, Cq), 131.3 (d, *J* = 5.5 Hz, CH), 129.3 (Cq), 122.9 (CH), 122.7 (d, *J* = 17.2 Hz, CH) 113.8 (d, *J* = 22.4 Hz, CH), 72.7 (CH_2), 67.8 (CH_2), 50.5 (CH), 48.5 (CH), 14.1 (d, *J* = 3.4 Hz, CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.6. **HRMS** calcd for $C_{24}H_{24}F_2KO_2$ $[M+K]^+$ 421.1376, found 421.1379.

(3a*R*,4*S*,5*R*,5a*S*)-4,5-bis(3-fluoro-4-methylphenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22d' was isolated with 15 % yield (white solid, 11.5 mg, 0.03 mmol) following **GP-3** using **20d** (76.5 mg, 0.2 mmol) as a substrate. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.95 – 9.90 (m, 2H), 6.37 – 6.33 (m, 4H), 4.39 (q, *J* = 12.8, 11.9 Hz, 4H), 4.12 (t, *J* = 7.9 Hz, 2H), 3.28 (dd, *J* = 10.3, 7.9 Hz, 2H), 3.07 (brs, 2H), 2.78 (d, *J* = 5.1 Hz, 2H), 2.21 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.9 (d, *J* = 244.3 Hz, Cq), 140.8 (d, *J* = 7.1 Hz, Cq), 131.9 (Cq), 130.7 (d, *J* = 5.5 Hz, CH), 124.1 (d, *J* = 3.3 Hz, CH), 122.9 (d, *J* = 17.3 Hz, Cq), 115.1 (d, *J* = 22.3 Hz, CH), 72.0 (CH_2), 68.3 (CH_2), 46.6 (CH), 42.6 (CH), 14.2 (d, *J* = 3.5 Hz, CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -118.0. **HRMS** calcd for $C_{24}H_{24}F_2KO_2$ $[M+K]^+$ 421.1376, found 421.1372.

(1*S*,1'*S*,5*R*,5'*R*,6*S*,6'*S*)-6,6'-bis(4-(trifluoromethyl)phenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21e was isolated with 20 % yield (white solid, 18.3 mg, 0.04 mmol) following **GP-3** using **20e** (91mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, C_6D_6, 318 K) δ 7.25 (brs, 4H), 6.58 (brs, 4H), 3.61 (d, *J* = 8.3 Hz, 2H), 3.50 – 3.48 (brs, 2H), 3.35 (d, *J* = 8.4 Hz, 2H), 2.82 (brs, 2H), 1.71 – 1.70 (m, 2H), 1.23 – 1.21 (m, 2H). **^{13}C NMR** (101 MHz, C_6D_6, 318 K) δ 141.8 (Cq), 130.0 (Cq), 126.4 (2CH), 125.1 (d, *J* = 271.6 Hz, Cq), 125.1 (2CH), 73.6 (CH_2), 69.4 (CH_2), 34.4 (Cq), 29.6 (CH), 27.6 (CH). **^{19}F NMR** (376 MHz, C_6D_6, 318 K) δ -62.2. **HRMS** calcd for $C_{24}H_{21}F_6O_2$ $[M+H]^+$ 455.1440, found 455.1442.

(1*R*,1'*S*,5*S*,5'*R*,6*R*,6'*S*)-6,6'-bis(4-(trifluoromethyl)phenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21e' was isolated with 22 % yield (white solid, 20 mg, 0.04 mmol) following **GP-3** using **20e** (91mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 4H), 7.13 (d, *J* = 8.0 Hz, 4H), 3.88 (d, *J* = 8.5 Hz, 2H), 3.72 (dd, *J* = 8.5, 2.8 Hz, 2H), 3.60 – 3.53 (m, 4H), 2.07 (d, *J* =

4.6 Hz, 2H), 1.69 – 1.67 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2 (Cq), 128.7 (q, *J* = 32.6 Hz, Cq), 127.9 (2CH), 125.1 (q, *J* = 3.8 Hz, 2CH), 124.1 (q, *J* = 271.9 Hz, CF_3), 74.0 (CH_2), 69.9 (CH_2), 34.5 (Cq), 30.1 (CH), 28.2 (CH). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.3. **HRMS** calcd for $C_{24}H_{21}F_6O_2$ $[M+H]^+$ 455.1440, found 455.1447.

(3a*S*,4*R*,5*R*,5a*S*)-4,5-bis(4-(trifluoromethyl)phenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22e was isolated with 18 % yield (white solid, 16.3 mg, 0.04 mmol) following **GP-3** using **20e** (91mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.8 Hz, 4H), 7.12 (d, *J* = 7.9 Hz, 4H), 4.46 (d, *J* = 12.1 Hz, 2H), 4.30 (d, *J* = 12.4 Hz, 2H), 3.82 (t, *J* = 6.4 Hz, 2H), 3.37 (d, *J* = 9.1 Hz, 2H), 3.06 (brs, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.2 (Cq), 129.4 (Cq), 129.1 (q, *J* = 32.6 Hz, Cq), 127.7 (2CH), 125.6 (q, *J* = 3.3 Hz, 2CH), 123.9 (q, *J* = 272.1 Hz, CF_3), 72.4 (CH_2), 67.8 (CH_2), 50.3 (CH), 48.9 (CH). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.6. **HRMS** calcd for $C_{24}H_{21}F_6O_2$ $[M+H]^+$ 455.1440, found 455.1441.

(3a*R*,4*S*,5*R*,5a*S*)-4,5-bis(4-(trifluoromethyl)phenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22e' was isolated with 17 % yield (white solid, 15.7 mg, 0.03 mmol) following **GP-3** using **20e** (91mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 4H), 6.78 (d, *J* = 8.0 Hz, 4H), 4.43 (dt, *J* = 14.5, 11.4 Hz, 4H), 4.14 (t, *J* = 7.9 Hz, 2H), 3.31 (dd, *J* = 10.2, 8.0 Hz, 2H), 3.13 (brs, 2H), 2.94 (d, *J* = 4.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9 (Cq), 132.0 (Cq), 129.3 (q, *J* = 32.4 Hz, Cq), 129.0 (2CH), 125.0 (q, *J* = 3.7 Hz, 2CH), 124.0 (q, *J* = 272.0 Hz, CF_3), 71.8 (CH_2), 68.3 (CH_2), 47.0 (CH), 42.4 (CH). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.5. **HRMS** calcd for $C_{24}H_{21}F_6O_2$ $[M+H]^+$ 455.1440, found 455.1438.

(1*S*,1'*S*,5*R*,5'*R*,6*S*,6'*S*)-6,6'-bis(3-(trifluoromethyl)phenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21f was isolated with 16 % yield (white solid, 14.7 mg, 0.03 mmol) following **GP-3** using **20f** (91mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, C_6D_6, 333 K) δ 7.20 – 7.14 (m, 4H), 6.84 – 6.81 (m, 2H), 6.72 (brs, 2H), 3.60 (d, *J* = 8.3 Hz, 2H), 3.50 (d, *J* = 8.3 Hz, 2H), 3.32 (d, *J* = 8.3 Hz, 2H), 2.91 (brs, 2H), 1.74 (d, *J* = 4.6 Hz, 2H), 1.34 (d, *J* = 3.8 Hz, 2H). **^{13}C NMR** (101 MHz, C_6D_6, 318 K) δ 138.4 (Cq), 131.5 (CH), 130.3 (q, *J* = 31.9 Hz, Cq), 128.7 (CH), 128.2 (CH), 124.5 (d, *J* = 272.3 Hz, CF_3), 122.5 (CH), 73.1 (CH_2), 68.9 (CH_2), 33.9 (Cq), 29.5 (CH), 27.1 (CH). **^{19}F NMR** (376 MHz, C_6D_6, 318 K) δ -62.2. **HRMS** calcd for $C_{24}H_{21}F_6O_2$ $[M+H]^+$ 455.1440, found 455.1442.

(1*R*,1'*S*,5*S*,5'*R*,6*R*,6'*S*)-6,6'-bis(3-(trifluoromethyl)phenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21f' was isolated with 16 % yield (white solid, 14.6 mg, 0.03 mmol) following **GP-3** using **20f** (91mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.51 (m, 2H), 7.47 – 7.43 (m, 2H), 7.29 – 7.26 (m, 2H), 7.20 (brs, 2H), 3.86 (d, *J* = 8.5 Hz, 2H), 3.72 (dd, *J* = 8.5, 2.8 Hz, 2H), 3.60 – 3.52 (m, 4H), 2.06 (d, *J* = 4.6 Hz, 2H), 1.66 – 1.64 (brs, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.9 (Cq), 131.7 (CH), 130.72 (q, *J* = 32.2 Hz, Cq), 128.7 (CH), 124.1 (q, *J* = 272.4 Hz, CF_3), 123.61 (d, *J* = 3.8 Hz, CH), 123.16 (d, *J* = 4.2 Hz, CH), 74.0 (CH_2), 69.8 (CH_2), 34.2 (Cq), 30.0 (CH), 27.8 (CH). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.4. **HRMS** calcd for $C_{24}H_{21}F_6O_2$ $[M+H]^+$ 455.1440, found 455.1445.

(3a*S*,4*R*,5*R*,5a*S*)-4,5-bis(3-(trifluoromethyl)phenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22f was isolated with 16 % yield (white solid, 14.5 mg, 0.03 mmol) following **GP-3** using **20f** (91mg, 0.2 mmol) as a substrate. **^{1}H NMR** (300 MHz, $CDCl_3$) 7.32 – 7.14 (m, 8H), 4.49 (d, *J* = 12.8 Hz, 2H), 4.31 (d, *J* = 11.3 Hz, 2H), 3.87 (t, *J* = 7.3 Hz, 2H), 3.38 (dd, *J* = 10.9, 7.7

Hz, 2H), 3.19 – 3.15 (m, 2H), 3.01 – 2.98 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.0 (Cq),131.1 (Cq), 130.7 (Cq), 129.4 (CH), 129.0 (CH), 124.2 (m, CH), 123.81 (d, *J* = 272.4 Hz, CF_3), 123.62 (d, *J* = 3.5 Hz, CH), 72.4 (CH_2), 67.8 (CH_2), 49.7 (CH), 49.4 (CH).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.9. **HRMS** calcd for $C_{24}H_{21}F_6O_2$ $[M+H]^+$ 455.1440, found 455.1442.

(3a*R*,4*S*,5*R*,5a*S*)-4,5-bis(3-(trifluoromethyl)phenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22f' was isolated with 16 % yield (white solid, 14.7 mg, 0.03 mmol) following **GP-3** using **20f** (91mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.30 – 7.26 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.75 (brs, 2H), 4.47 (dd, *J* = 11.7, 2.2 Hz, 2H), 4.40 (d, *J* = 11.5 Hz, 2H), 4.15 (t, *J* = 7.9 Hz, 2H), 3.33 (dd, *J* = 10.3, 8.0 Hz, 2H), 3.13 (brs, 2H), 2.94 (d, *J* = 5.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.6 (Cq), 131.8 (CH), 131.8 (CH), 130.4 (q, *J* = 32.2 Hz, Cq), 128.6 (CH), 125.4 (d, *J* = 3.8 Hz, CH), 123.8 (q, *J* = 272.0 Hz, CF_3), 123.6 (q, *J* = 3.9 Hz, Cq), 71.9 (CH_2), 68.3 (CH_2), 47.1 (CH), 42.2 (CH). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.9. **HRMS** calcd for $C_{24}H_{21}F_6O_2$ $[M+H]^+$ 455.1440, found 455.1441.

(1*S*,1'*S*,5*R*,5'*R*,6*S*,6'*S*)-6,6'-di(naphthalen-2-yl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21g was isolated with 24 % yield (white solid, 20 mg, 0.05 mmol) following **GP-3** using **20g** (84 mg, 0.2 mmol) as a substrate. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.19 – 7.31 (m, 14H), 3.87 (d, *J* = 8.1 Hz, 2H), 3.61 (dd, *J* = 12.7, 8.0 Hz, 4H), 2.69 (brs, 2H), 2.16 (d, *J* = 4.7 Hz, 2H), 2.03 – 1.84 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.4 (Cq), 133.3 (Cq), 132.0 (Cq), 127.7 (CH), 127.6 (2CH), 127.3 (CH), 127.0 (CH), 126.2 (CH), 125.5 (CH), 73.2 (CH_2), 69.2 (CH_2), 34.4 (Cq), 29.3 (CH), 27.5 (CH). **HRMS** calcd for $C_{30}H_{26}KO_2$ $[M+K]^+$ 457.1564, found 457.1564.

(1*R*,1'*S*,5*S*,5'*R*,6*R*,6'*S*)-6,6'-di(naphthalen-2-yl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 21g' was isolated with 23 % yield (white solid, 19 mg, 0.05 mmol) following **GP-3** using **20g** (84 mg, 0.2 mmol) as a substrate. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (td, *J* = 7.9, 1.7 Hz, 6H), 7.61 – 7.35 (m, 6H), 7.31 – 7.19 (m, 2H), 3.84 (d, *J* = 8.3 Hz, 2H), 3.75 (dd, *J* = 8.3, 2.8 Hz, 2H), 3.68 (d, *J* = 8.6 Hz, 2H), 3.58 (d, *J* = 8.6 Hz, 2H), 2.13 (d, *J* = 4.7 Hz, 2H), 1.79 (dd, *J* = 4.8, 2.8 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.4 (Cq), 133.3 (Cq), 132.1 (Cq), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.4 (CH), 125.8 (CH), 125.5 (CH), 74.2 (CH_2), 70.1 (CH_2), 34.4 (Cq), 30.5 (CH), 27.5 (CH). **HRMS** calcd for $C_{30}H_{26}KO_2$ $[M+K]^+$ 457.1564, found 457.1567.

(3a*S*,4*R*,5*R*,5a*S*)-4,5-di(naphthalen-2-yl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22g was isolated with 8 % yield (white solid, 7.5 mg, 0.02 mmol) following **GP-3** using **20g** (84 mg, 0.2 mmol) as a substrate. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 6H), 7.50 (s, 2H), 7.36 – 7.23 (m, 6H), 4.50 (d, *J* = 12.3 Hz, 2H), 4.34 (d, *J* = 11.4 Hz, 2H), 3.83 (t, *J* = 6.9 Hz, 2H), 3.47 (dd, *J* = 10.0, 7.6 Hz, 2H), 3.28 (brs, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.1 (Cq), 133.3 (Cq), 132.2 (Cq), 129.5 (Cq), 128.2 (CH), 127.5 (CH), 127.4 (CH), 126.5 (CH), 125.8 (CH), 125.3 (2CH), 72.9 (CH_2), 67.9 (CH_2), 50.6 (CH), 49.2 (CH). **HRMS** calcd for $C_{30}H_{26}KO_2$ $[M+K]^+$ 457.1564, found 457.1566.

(3a*R*,4*S*,5*R*,5a*S*)-4,5-di(naphthalen-2-yl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 22g' was isolated with 10 % yield (white solid, 8 mg, 0.02 mmol) following **GP-3** using **20g** (84 mg, 0.2 mmol) as a substrate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.72 (m, 2H), 7.57 – 7.55 (m, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.42 – 7.38 (m, 4H), 7.21 – 7.08 (m, 2H), 6.69 (dd, *J* = 8.5, 1.8 Hz, 2H), 4.74 – 4.36 (m, 4H), 4.17 (t, *J* = 7.1 Hz, 2H), 3.38 (q, *J* =

10.5 Hz, 4H), 3.11 (d, *J* = 4.5 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.8 (Cq), 133.1 (Cq), 132.2 (Cq), 132.2 (Cq), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.4 (CH), 127.2 (CH), 125.8 (CH), 125.5 (CH), 72.1 (CH_2), 68.4 (CH_2), 47.5 (CH), 42.9 (CH). **HRMS** calcd for $C_{30}H_{26}KO_2$ $[M+K]^+$ 457.1564, found 457.1561.

(1*S*,5*R*,6*S*)-6-phenyl-1-((1*S*,5*R*,6*S*)-6-phenyl-3-oxabicyclo[3.1.0]hexan-1-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane 21h (1*S*,5*R*,6*S*)-6-phenyl-1-((1*R*,5*S*,6*R*)-6-phenyl-3-oxabicyclo[3.1.0]hexan-1-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane 21h' (3a*R*,4*S*,5*R*,5a*S*)-4,5-diphenyl-7-tosyl-3,3a,4,5,5a,6,7,8-octahydro-1*H*-furo[3,4-*e*]isoindole 22h' were isolated with 66 % yield (62 mg, 0.131 mmol) following the **GP-3** using **20h** (94 mg, 0.2 mmol) as reagent. **^{13}C NMR** ratio 49:27:24 for **21h : 21h'' : 22h'**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.36 -7.07 (m, 21H), 7.41 (d, *J* = 7.9 Hz, 2H), 6.93 – 6.79 (m, 9H), 6.58 (d, *J* = 7.3 Hz, 2H), 6.54 (d, *J* = 7.2 Hz, 2H), 4.42 (dd, *J* = 12.9, 1.9 Hz, 1H), 4.28 (dd, *J* = 13.0, 2.3 Hz, 1H), 4.04 (t, *J* = 7.9 Hz, 1H), 4.00 (ddd, *J* = 13.3, 3.4, 1.6 Hz, 1H), 3.87 (dd, *J* = 13.5, 1.9 Hz, 1H), 3.79 (d, *J* = 8.5 Hz, 2H), 3.76 (d, *J* = 8.1 Hz, 1H), 3.73 (d, *J* = 8.8 Hz, 1H), 3.69 (dd, *J* = 8.3, 2.8 Hz, 1H), 3.58 (d, *J* = 8.8 Hz, 1H), 3.55 (d, *J* = 8.1 Hz, 1H), 3.53 (d, *J* = 8.1 Hz, 1H), 3.46 (d, *J* = 9.7 Hz, 1H), 3.42 (d, *J* = 10.2 Hz, 1H), 3.38 (d, *J* = 8.8 Hz, 1H), 3.35 (d, *J* = 8.7 Hz, 1H), 3.18 (d, *J* = 8.7 Hz, 1H), 3.13 (dd, *J* = 10.3, 8.0 Hz, 1H), 3.09 (d, *J* = 10.1 Hz, 1H),3.08 – 2.99 (m, 4H), 2.89 (d, *J* = 8.8 Hz, 1H), 2.79 – 2.75 (m, 1H), 2.63 – 2.61 (m, 2H), 2.53 (s, 3H), 2.50 (s, 3H), 2.43 (s, 3H), 2.23 (d, *J* = 4.4 Hz, 1H), 2.01 – 1.99 (m, 1H), 1.93 (d, *J* = 4.7 Hz, 1H), 1.91 (d, *J* = 4.7 Hz, 1H), 1.69 (d, *J* = 4.7 Hz, 1H), 1.66 – 1.63 (m, 1H), 1.59 – 1.57 (m, 1H), 1.29 – 1.28 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.7 (2Cq), 143.7 (Cq), 143.3 (Cq), 140.6 (Cq), 140.5 (Cq), 137.4 (Cq), 137.1 (Cq), 136.0 (Cq), 135.9 (Cq), 134.8 (Cq), 133.8 (Cq), 133.6 (Cq), 133.2 (Cq),

129.8 (2CH), 129.7 (2CH), 129.6 (2CH), 129.1 (2CH), 128.8 (2CH), 128.6 (2CH), 128.5 (2CH), 128.2 (2CH), 128.2 (2CH), 128.1 (2CH), 127.8 (2CH), 127.8 (2CH), 127.8 (2CH), 127.6 (2CH), 127.5 (3CH), 127.5 (2CH), 126.6 (CH), 126.5 (CH), 126.5 (CH), 126.4 (2CH), 126.3 (2CH), 125.8 (2CH), 73.7 (CH_2), 72.5 (CH_2), 72.2 (CH_2), 69.8 (CH_2), 69.0 (CH_2), 68.4 (CH_2), 55.2 (CH_2), 53.2 (CH_2), 52.1 (CH_2), 50.5 (CH_2), 49.3 (CH_2), 49.1 (CH_2), 47.8 (CH), 46.7 (CH), 42.6 (CH), 41.4 (CH), 34.9 (Cq), 34.8 (Cq), 33.2 (Cq), 32.3 (Cq), 31.0 (2CH), 28.3 (CH), 27.6 (CH), 27.4 (CH), 27.1 (CH), 26.9 (CH), 26.8 (CH), 21.6 (CH_3), 21.5 (CH_3), 21.5 (CH_3). **HRMS** cald for $C_{29}H_{29}KNO_3S$ $[M+K]^+$ 663.1748, found 663.1750.

(3a*R*,4*R*,5*R*,5a*R*)-4,5-diphenyl-7-tosyl-3,3a,4,5,5a,6,7,8-octahydro-1*H*-furo[3,4-*e*]isoindole 22h was isolated with 13 % yield (12.4 mg, 0.026 mmol) following the **GP-3** using **20h** (94 mg, 0.2 mmol) as reagent. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.11 – 6.98 (m, 6H), 6.92 – 6.91 (m, 4H), 4.36 (d, *J* = 13.1 Hz, 1H), 4.25 (d, *J* = 13.1 Hz, 1H), 4.05 (d, *J* = 14.1 Hz, 1H), 3.78 (t, *J* = 7.6 Hz, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 3.48 (dd, *J* = 9.1, 7.1 Hz, 1H), 3.32 (dd, *J* = 10.8, 7.9 Hz, 1H), 3.00 – 2.94 (m, 2H), 2.83 (p, *J* = 10.9 Hz, 2H), 2.71 (dd, *J* = 11.1, 9.1 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.6 (Cq), 141.1 (Cq), 140.6 (Cq), 133.8 (Cq), 131.9 (Cq), 129.8 (2CH), 128.4 (2CH), 128.3 (2CH), 127.5 (2CH), 127.4 (2CH), 126.6 (CH), 126.4 (CH), 126.0 (Cq), 72.8 (CH_2), 67.8 (CH_2), 53.1 (CH_2), 49.9 (CH), 49.9 (CH), 49.2 (CH), 49.0 (CH), 48.8 (CH_2), 21.6 (CH_3). **HRMS** cald for $C_{29}H_{29}KNO_3S$ $[M+K]+$ 663.1748, found 663.1750.

(1*S*,1'*S*,5*R*,5'*R*,6*S*,6'*S*)-6,6'-diphenyl-3,3'-ditosyl-3,3'-diaza-1,1'-bi(bicyclo[3.1.0]hexane) 21i, **(1*R*,1'*S*,5*S*,5'*R*,6*R*,6'*S*)-6,6'-diphenyl-3,3'-ditosyl-3,3'-diaza-1,1'-bi(bicyclo[3.1.0]hexane) 21i'**, **(3a*S*,4*R*,5*R*,5a*S*)-4,5-**

diphenyl-2,7-ditosyl-1,2,3,3a,4,5,5a,6,7,8-decahydropyrrolo[3,4-*e*]isoindole 22j and **(3a*R*,4*S*,5*R*,5a*S*)-4,5-diphenyl-2,7-ditosyl-1,2,3,3a,4,5,5a,6,7,8-decahydropyrrolo[3,4-*e*]isoindole 22j'** were isolated with 74 % yield (46.2 mg, 0.074 mmol) following the **GP-3** using **20j** (62.5 mg, 0.1 mmol) as reagent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 10H), 7.61 – 7.59 (m, 6H), 7.41 – 7.32 (m, 20H), 7.24 – 7.22 (m, 9H), 7.11 – 7.07 (m, 10H), 6.88 – 6.84 (m, 6H), 6.68 – 6.66 (m, 6H), 6.49 – 6.47 (m, 4H), 4.14 (q, *J* = 7.1 Hz, 4H), 4.01 – 3.98 (m, 4H), 3.83 (d, *J* = 13.4 Hz, 2H), 3.67 – 3.62 (m, 4H), 3.47 – 3.42 (m, 6H), 3.11 – 3.05 (m, 6H), 2.90 – 2.86 (m, 9H), 2.76 – 2.73 (m, 2H), 2.66 – 2.60 (m, 8H), 2.51 (s, 12H), 2.47 (s, 6H), 2.44 (s, 6H), 1.67 (d, *J* = 4.7 Hz, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.8 (Cq), 143.8 (2Cq), 143.7 (Cq), 143.4 (Cq), 140.2 (Cq), 139.9 (Cq), 136.5 (Cq), 135.3 (Cq), 133.6 (Cq), 133.4 (Cq), 133.0 (Cq), 130.6 (Cq), 129.9 (2CH), 129.8 (2CH), 129.7 (6CH), 129.6 (CH), 128.7 (CH), 128.6 (2CH), 128.4 (Cq), 128.3 (2CH), 128.2 (2CH), 127.8 (2CH), 127.5 (4CH), 127.4 (8CH), 126.7 (2CH), 126.7 (2CH), 60.3 (CH_2), 54.6 (CH_2), 52.9 (CH_2), 52.0 (CH_2), 50.2 (CH_2), 49.4 (CH), 49.4 (CH_2), 48.9 (CH_2), 48.7 (CH), 47.2 (CH), 41.4 (CH), 33.9 (2Cq), 31.5 (CH), 29.6 (CH_2), 29.2 (CH), 26.9 (CH), 26.5 (CH), 21.5 ($2CH_3$), 21.5 ($2CH_3$).**HRMS** cald for $C_{36}H_{36}KN_2O_4S_2$ [M+K]+ 663.1748, found 663.1750.

(1*S*,1'*S*,5*R*,5'*R*,6*S*)-6-phenyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24a and **(1*R*,1'*S*,5*S*,5'*R*,6*R*)-6-phenyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24a'** were isolated with 69 % yield (33.4 mg, 0.14 mmol) following the **GP-4** using **23a** (48.5 mg, 0.2 mmol) as reagent. **^{1}H NMR** ratio 1:1.26 for **24a** (*m*): **24a'** (*M*) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 5H m), 7.20 – 7.16 (m, 5H M), 4.10 (d, *J* = 8.2 Hz, 1H m), 3.99 (d, *J* = 8.2 Hz, 1H M), 3.96 (dd, *J* = 8.3, 5.8 Hz, 1H M, 1 m), 3.81 (ddd, *J* = 8.5, 6.0, 3.0 Hz, 1H M, 1 m), 3.76 (d, *J* = 8.2 Hz, 1H M), 3.73 (d, *J* = 8.2 Hz, 1H m), 3.69 (d, *J* = 8.3 Hz, 1H m), 3.64 (dd, *J* = 8.3, 2.9

Hz, 1H m), 3.57 (d, *J* = 7.7 Hz, 1H M), 3.46 – 3.37 (m, 1H m, 2H M), 3.35 (d, *J* = 8.2 Hz, 1H m), 2.77 (dd, *J* = 8.0, 2.8 Hz, 1H M), 2.29 (d, *J* = 4.5 Hz, 1H M), 2.23 (d, *J* = 4.5 Hz, 1H m), 1.94 (dd, *J* = 4.5, 2.9 Hz, 1H m), 1.85 (dd, *J* = 4.5, 3.0 Hz, 1H M), 1.67 (brs, 1H m), 1.28 (ddd, *J* = 7.8, 4.6, 2.8 Hz, 1H M), 1.07 (ddd, *J* = 7.6, 4.5, 2.8 Hz, 1H M), 0.47 (tdd, *J* = 12.6, 8.0, 4.7 Hz, 1H m, 1H M), 0.39 (t, *J* = 4.7 Hz, 1H m). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.5 (Cq m), 136.8 (Cq M), 129.1 (2CH M), 128.5 (2CH m), 128.1 (2CH M), 128.1 (2CH m), 126.2 (CH M), 126.0 (CH m), 74.1 (CH_2 M), 73.7 (CH_2 m), 71.6 (CH_2 m), 71.3 (CH_2 M), 70.1 (CH_2 m), 69.9 ($2CH_2$ M), 68.8 (CH_2 m), 36.5 (Cq m), 36.3 (Cq M), 30.0 (CH m), 29.5 (CH M), 26.7 (CH), 26.5 (CH), 26.4 (Cq), 26.2 (Cq), 25.2 (CH), 21.3 (CH), 15.2 (CH_2 m), 11.0 (CH_2 M). **HRMS** cald for $C_{16}H_{18}NaO_2$ $[M+Na]^+$ 265.1199, found 265.1197

(3a*S*,4*R*,5a*S*)-4-phenyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran 25a and **(3a*S*,4*R*,5a*R*)-4-phenyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran 25a'** were isolated with 25 % yield (12.3 mg, 0.05 mmol) following the **GP-4** using **23a** (48.5 mg, 0.2 mmol) as reagent. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 4H), 7.25 – 7.18 (m, 6H), 4.41 – 4.38 (m, 2H), 4.36 – 4.29 (m, 2H), 4.28 – 4.18 (m, 4H), 4.12 (t, *J* = 7.8 Hz, 1H), 4.01 (t, *J* = 8.3 Hz, 1H), 3.96 (t, *J* = 7.5 Hz, 1H), 3.33 – 3.25 (m, 4H), 2.88 – 2.85 (m, 4H), 2.62 (ddd, *J* = 12.4, 10.2, 2.5 Hz, 1H), 2.30 (ddd, *J* = 11.8, 9.3, 5.1 Hz, 1H), 2.14 (ddd, *J* = 12.5, 5.2, 2.4 Hz, 1H), 1.95 (ddd, *J* = 14.3, 11.8, 8.6 Hz, 1H), 1.79 (ddd, *J* = 14.3, 5.1, 2.3 Hz, 1H), 1.61 – 1.55 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.5 (Cq), 144.4 (Cq), 132.5 (Cq), 130.0 (Cq), 129.9 (Cq), 129.8 (Cq), 128.7 (2CH), 128.7 (2CH), 127.3 (2CH), 126.7 (CH), 126.6 (3CH), 73.2 (CH_2), 73.2 (CH_2), 72.9 (CH_2), 72.0 (CH_2), 68.9 (CH_2), 67.7 (CH_2), 67.5 (CH_2), 67.2 (CH_2), 48.1 (CH), 45.2 (CH), 43.7 (CH), 43.5 (CH), 42.8 (CH), 38.2 (CH), 32.4

(CH_2), 30.8 (CH_2). **HRMS** cald for $C_{16}H_{18}KO_2$ [M+K]+ 281.0938, found 281.0936.

(1*S*,1'*S*,5*R*,5'*R*,6*S*)-6-(*o*-tolyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24b (Major **M**) and **(1*R*,1'*S*,5*S*,5'*R*,6*R*)-6-(*o*-tolyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24b'** (minor **m**) were isolated with 40 % yield (20 mg, 0.08 mmol) following the **GP-4** using **23b** (51 mg, 0.2 mmol) as reagent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 3H M, 3H m), 7.00 – 6.98 (1H M, 1H m), 4.16 (d, *J* = 8.2 Hz, 1H M), 4.03 (d, *J* = 8.2 Hz, 1H m), 3.96 – 3.92 (m, 1H M, 1H m), 3.85 – 3.81 (m, 1H M, 1H m), 3.79 – 3.76 (m 1H M, 1H m), 3.66 (d, *J* = 8.2 Hz, 1H M), 3.61 (dd, *J* = 8.2, 2.8 Hz, 2H m), 3.46 (ddd, *J* = 10.6, 9.4, 7.8 Hz, 2H M), 3.33 (d, *J* = 8.0 Hz, 1H M), 3.15 (d, *J* = 7.7 Hz, 1H m), 2.71 (dd, *J* = 8.0, 2.8 Hz, 1H m), 2.40 (s, 3H m), 2.34 (s, 3H M), 2.19 – 2.17 (m 1H M, 1H m), 2.03 (dd, *J* = 4.7, 3.0 Hz, 1H M), 1.97 (dd, *J* = 4.8, 3.0 Hz, 1H m), 1.26 – 1.17 (m, 1H M, 1H m), 0.45 – 0.40 (m, 2H M, 1H m), 0.26 (t, *J* = 4.9 Hz, 1H m). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.8 (Cq m), 137.6 (Cq M), 135.3 (Cq M), 134.8 (Cq m), 130.1 (CH m), 129.8 (CH M), 127.0 (CH M), 127.0 (CH m), 126.2 (1 CH M, 1 CH m), 125.4 (CH M), 125.3 (CH m), 74.1 (CH_2 m), 73.6 (CH_2 M), 71.4 (CH_2 M), 70.9 (CH_2 m), 70.1 (CH_2 M), 70.0 (CH_2 m), 69.8 (CH_2 M), 68.6 (CH_2 m), 36.3 (Cq M), 36.3(Cq m), 28.2 (CH M), 27.9 (CH m), 26.5 (CH M), 26.2 (Cq m), 26.2 (Cq M), 25.6 (CH M), 25.3 (CH m), 21.1 (CH M), 20.1 (CH_3 m), 19.8 (CH_3 M), 14.8 (CH_2 M), 10.8 (CH_2 m). **HRMS** cald for $C_{17}H_{20}NaO_2$ $[M+Na]^+$ 279.1356, found 279.1358.

(3a*S*,4*R*,5a*S*)-4-(*o*-tolyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 25b and **(3a*S*,4*R*,5a*R*)-4-(*o*-tolyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 25b'** were isolated with 25 % yield (13.3 mg, 0.052 mmol) following the **GP-4** using **23b** (51 mg, 0.2 mmol) as reagent.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.41 – 7.09 (m, 8H), 4.40 – 4.18 (m, 8H), 4.14 (t, *J* = 7.4 Hz, 1H), 4.08 (t, *J* = 7.8 Hz, 1H), 4.01 (t, *J* = 8.2 Hz, 1H), 3.89 (t, *J* = 7.3 Hz, 1H), 3.26 – 3.14 (m, 3H), 3.03 – 2.96 (m, 2H), 2.90 (td, *J* = 10.9, 10.5, 2.3 Hz, 1H), 2.84- 2.79 (m, 1H), 2.60 (ddd, *J* = 10.8, 9.3, 5.4 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.01 (ddd, *J* = 12.5, 5.3, 2.3 Hz, 1H), 1.78 – 1.71 (m, 3H), 1.47 (dt, *J* = 12.5, 11.1 Hz, 2H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 143.2 (Cq), 143.1 (Cq), 136.1 (Cq), 135.8 (Cq), 133.3 (2Cq), 130.8 (CH), 130.8 (CH), 130.5 (Cq), 130.4 (CH), 130.3 (Cq), 129.0 (CH), 126.8 (2CH), 126.5 (CH), 126.4 (CH), 73.5 (CH_2), 73.3 (CH_2), 72.8 (CH_2), 72.3 (CH_2), 69.2 (CH_2), 67.9 (CH_2), 67.8 (CH_2), 67.5 (CH_2), 48.2 (CH), 45.1 (CH), 43.5 (CH), 39.0 (CH), 38.6 (CH), 33.0 (CH), 30.5 (CH_2), 30.1 (CH_2), 19.8 (CH_3), 19.6 (CH_3). **HRMS** cald for $C_{17}H_{20}KO_2$ [M+K]+ 295.1095, found 295.1097.

(1*S*,1'*S*,5*R*,5'*R*,6*S*)-6-(3-fluoro-4-methylphenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24c and **(1*R*,1'*S*,5*S*,5'*R*,6*R*)-6-(3-fluoro-4-methylphenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24c'** were isolated with 53 % yield (28.8 mg, 0.105 mmol) following the **GP-4** using **23c** (54.8 mg, 0.2 mmol) as reagent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.10 – 7.03 (m, 2H), 6.88 – 6.79 (m, 4H), 4.08 (d, *J* = 8.2 Hz, 1H), 3.97 – 3.92 (m, 3H), 3.78 (dt, *J* = 8.3, 2.8 Hz, 2H), 3.75 – 3.70 (m, 3H), 3.65 (dd, *J* = 8.3, 2.8 Hz, 1H), 3.57 (d, *J* = 7.8 Hz, 1H), 3.49 (d, *J* = 8.0 Hz, 1H), 3.43 – 3.34 (m, 3H), 2.89 (dd, *J* = 8.0, 2.8 Hz, 1H), 2.23 (s, 3H), 2.23 (s, 3H), 2.19 (dd, *J* = 11.8, 4.4 Hz, 1H), 1.86 (dd, *J* = 4.4, 2.9 Hz, 1H), 1.78 (dd, *J* = 4.4, 2.9 Hz, 1H), 1.74 (brs, 1H), 1.31 (ddd, *J* = 7.8, 4.6, 2.8 Hz, 1H), 1.12 (ddd, *J* = 7.6, 4.4, 2.7 Hz, 1H), 0.51 – 0.41 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1 (d, *J* = 244.4 Hz, Cq), 161.0 (d, *J* = 244.1 Hz, Cq), 137.3 (d, *J* = 7.7 Hz, Cq), 136.6 (d, *J* = 7.6 Hz, Cq), 131.0 (d, *J* = 5.1 Hz, CH), 131.0 (d, *J* = 5.4 Hz, CH), 124.5 (d, *J* = 3.1 Hz, CH), 124.0 (d, *J* = 3.1 Hz, CH), 122.4 (d, *J* = 17.2 Hz, Cq), 122.3 (d, *J* = 17.3 Hz, Cq), 115.4 (d, *J* = 22.5

Hz, CH), 114.9 (d, *J* = 22.4 Hz, CH), 74.0 (CH_2), 73.5 (CH_2), 71.5 (CH_2), 71.3 (CH_2), 69.9 ($2CH_2$), 69.8 (CH_2), 68.9 (CH_2), 36.6 (Cq), 36.5 (Cq), 29.4 (CH), 28.9 (CH), 27.0 (CH), 26.9 (CH), 26.4 (Cq), 26.1 (Cq), 25.2 (CH), 21.2 (CH), 15.3 (CH_2), 14.1 (CH_3), 14.1 (CH_3), 11.1 (CH_2). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -118.0, -118.2. **HRMS** cald for $C_{17}H_{19}FKO_2$ $[M+K]^+$ 313.1001, found 313.1003.

(3a*S*,4*R*,5a*S*)-4-(3-fluoro-4-methylphenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 25c and **(3a*S*,4*R*,5a*R*)-4-(3-fluoro-4-methylphenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 25c'** were isolated with 27 % yield (15 mg, 0.055 mmol) following the **GP-4** using **23c** (54.8 mg, 0.2 mmol) as reagent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.14 – 7.08 (m, 2H), 6.87 – 6.81 (m, 4H), 4.41 – 4.21 (m, 8H), 4.15 (dt, *J* = 24.3, 7.8 Hz, 2H), 3.99 (dt, *J* = 14.5, 7.8 Hz, 2H), 3.32 – 3.22 (m, 4H), 2.85 – 2.79 (m, 4H), 2.57 (t, *J* = 10.8 Hz, 1H), 2.25 (s, 6H), 2.14 – 2.08 (m, 1H), 1.96 – 1.84 (m, 1H), 1.79 – 1.73 (m, 1H), 1.65 (brs, 1H), 1.52 (q, *J* = 11.9 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.4 (d, *J* = 244.4 Hz, Cq), 161.4 (d, *J* = 244.6 Hz, Cq), 144.2 (Cq), 144.2 (Cq), 132.3 (Cq), 131.6 (d, *J* = 5.2 Hz, CH), 131.6 (d, *J* = 5.8 Hz, CH), 130.0 (d, *J* = 7.8 Hz, Cq), 129.6 (2Cq), 123.1 (d, *J* = 5.9 Hz, Cq), 122.9 (d, *J* = 5.5 Hz, Cq), 122.6 (d, *J* = 2.8 Hz, CH), 122.0 (d, *J* = 2.7 Hz, CH), 113.6 (d, *J* = 22.1 Hz, CH), 113.1 (d, *J* = 22.4 Hz, CH), 73.2 (CH_2), 73.1 (CH_2), 72.7 (CH_2), 71.9 (CH_2), 68.9 (CH_2), 67.7 (CH_2), 67.5 (CH_2), 67.2 (CH_2), 48.1 (CH), 45.2 (CH), 43.2 (CH), 43.0 (CH), 42.7 (CH), 38.1 (CH), 32.3 (CH_2), 30.7 (CH_2), 14.2 (CH_3), 14.1 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.2. **HRMS** cald for $C_{17}H_{19}FKO_2$ $[M+K]^+$ 313.1001, found 313.0998.

(1*S*,1'*S*,5*R*,5'*R*,6*S*)-6-(3-(trifluoromethyl)phenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24d and **(1*R*,1'*S*,5*S*,5'*R*,6*R*)-6-(3-(trifluoromethyl)phenyl)-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24d'** were

isolated with 45 % yield (28 mg, 0.09 mmol) following the **GP-4** using **23d** (62 mg, 0.2 mmol) as reagent. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 8H), 4.12 (d, *J* = 8.3 Hz, 1H), 4.00 (d, *J* = 8.4 Hz, 1H), 3.97 (dd, *J* = 8.4, 3.4 Hz, 2H), 3.81 (dd, *J* = 8.3, 3.0 Hz, 2H), 3.77 – 3.70(m, 3H), 3.66 (dd, *J* = 8.4, 2.9 Hz, 1H), 3.58 (d, *J* = 7.8 Hz, 1H), 3.48 (d, *J* = 8.2 Hz, 1H), 3.42 (dd, *J* = 8.1, 1.2 Hz, 1H), 3.33 (dd, *J* = 7.8, 1.1 Hz, 1H), 3.27 (d, *J* = 8.2 Hz, 1H), 2.79 (dd, *J* = 8.1, 2.8 Hz, 1H), 2.32 (d, *J* = 4.5 Hz, 1H), 2.28 (d, *J* = 4.4 Hz, 1H), 1.97 (dd, *J* = 4.5, 2.9 Hz, 1H), 1.91 (dd, *J* = 4.5, 2.9 Hz, 1H), 1.33 (ddd, *J* = 7.8, 4.7, 2.9 Hz, 1H), 1.10 (ddd, *J* = 8.2, 4.4, 2.7 Hz, 1H), 0.54 – 0.45 (m, 2H), 0.46 (dd, *J* = 8.2, 4.5 Hz, 1H), 0.40 (t, *J* = 4.8 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.8 (Cq), 138.2 (Cq), 132.8 (CH), 132.0 (CH), 130.57 (q, *J* = 32.1 Hz, Cq), 130.48 (q, *J* = 32.2 Hz, Cq), 128.6 (CH), 128.5 (CH), 125.3 (q, *J* = 3.6 Hz, CH), 125.1 (d, *J* = 4.1 Hz, CH), 124.1 (q, *J* = 272.5 Hz, CF_3), 124.1 (q, *J* = 273.9 Hz, CF_3), 122.9 (d, *J* = 3.9 Hz, CH), 122.8 (d, *J* = 3.8 Hz, CH), 74.0 (CH_2), 73.5 (CH_2), 71.4 (CH_2), 71.3 (CH_2), 69.9 ($2CH_2$), 69.8 (CH_2), 68.8 (CH_2), 37.0 (Cq), 36.8 (Cq), 29.6 (CH), 29.1 (CH), 27.1 (CH), 27.0 (CH), 26.2 (Cq), 26.0 (Cq), 25.2 (CH), 21.3 (CH), 15.3 (CH_2), 11.1 (CH_2). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.5, -62.6. **HRMS** cald for $C_{17}H_{17}F_3KO_2$ $[M+K]^+$ 349.0812, found 349.0815

(3a*S*,4*R*,5a*S*)-4-(3-(trifluoromethyl)phenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran 25d and **(3a*S*,4*R*,5a*R*)-4-(3-(trifluoromethyl)phenyl)-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c′*]difuran 25d'** were isolated with 19 % yield (12 mg, 0.04 mmol) following the **GP-4** using **23d** (62 mg, 0.2 mmol) as reagent. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.52 – 7.37 (m, 8H), 4.43 – 4.37 (m, 3H), 4.34 – 4.17 (m, 6H), 4.13 (t, *J* = 7.6 Hz, 1H), 4.02 – 3.93 (m, 3H), 3.33 – 3.26 (m, 3H), 2.89 – 2.84 (m, 4H), 2.69 (ddd, *J* = 12.4, 10.3, 2.4 Hz, 1H), 2.38 (ddd, *J* = 11.8, 9.3, 5.1 Hz, 1H), 2.15 (ddd, *J* = 12.5, 5.2, 2.4 Hz, 1H), 1.95 (ddd, *J* = 14.4, 11.8, 8.6 Hz, 1H), 1.80 (ddd, *J* =

14.3, 5.1, 2.3 Hz, 1H), 1.63 – 1.57 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.5 (2Cq), 145.4 (2Cq), 132.2 (2Cq), 130.7 (2Cq), 130.2 (CH), 130.1 (CH), 130.1 (CH), 129.5 (CH), 129.2 (CH), 129.2 (CH), 124.09 (q, *J* = 271.7 Hz, $2CF_3$), 123.98 (q, *J* = 3.8 Hz, CH), 123.61 (q, *J* = 3.3 Hz, CH), 73.1 (CH_2), 72.9 (CH_2), 72.5 (CH_2), 71.9 (CH_2), 68.9 (CH_2), 67.7 (CH_2), 67.5 (CH_2), 67.2 (CH_2), 48.0 (CH), 45.0 (CH), 43.6 (CH), 43.4 (CH), 42.7 (CH), 38.1 (CH), 32.3 (CH_2), 30.8 (CH_2). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.5. **HRMS** cald for $C_{17}H_{17}F_3KO_2$ $[M+K]^+$ 349.0812, found 349.0811.

(1*S*,5*R*,6*S*)-1-((1*R*,5*R*)-bicyclo[3.1.0]hexan-1-yl)-6-phenyl-3-oxabicyclo[3.1.0]hexane 24e and **(1*R*,5*S*,6*R*)-1-((1*R*,5*R*)-bicyclo[3.1.0]hexan-1-yl)-6-phenyl-3-oxabicyclo[3.1.0]hexane 24e'** were isolated with 67 % yield (32.2 mg, 0.13 mmol) following the **GP-4** using **23e** (48 mg, 0.2 mmol) as reagent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.16 (m, 10H), 4.11 (d, *J* = 8.1 Hz, 1H), 4.07 (d, *J* = 8.1 Hz, 1H), 3.95 (dd, *J* = 8.2, 6.6 Hz, 2H), 3.83 – 3.78 (m, 3H), 3.74 (d, *J* = 8.0 Hz, 1H), 2.22 (dd, *J* = 9.7, 4.4 Hz, 1H), 1.84 (dd, *J* = 4.4, 2.9 Hz, 1H), 1.77 (dd, *J* = 4.4, 3.0 Hz, 1H), 1.70 – 1.66 (m, 2H), 1.62 – 1.58 (m, 1H), 1.56 – 1.51 (m, 1H), 1.49 – 1.42 (m, 3H), 1.37 – 1.23 (m, 3H), 1.04 – 0.93 (m, 3H), 0.88 – 0.80 (m, 2H), 0.31 (t, *J* = 4.1 Hz, 1H), 0.26 – 0.18 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.4 (Cq), 137.6 (Cq), 129.1 (2CH), 128.8 (2CH), 127.8 (2CH), 127.7 (2CH), 125.6 (CH), 125.5 (CH), 74.7 (CH_2), 74.2 (CH_2), 70.4 (CH_2), 70.3 (CH_2), 40.2 (2Cq), 39.9 (2Cq), 31.3 (CH_2), 30.7 (CH_2), 30.3 (CH), 30.0 (CH), 27.7 (CH_2), 26.9 (CH), 26.7 (CH), 26.5 (CH_2), 25.7 (CH), 21.5 (CH), 21.1 (CH_2), 20.9 (CH_2), 14.3 (CH_2), 10.4 (CH_2). **HRMS** cald for $C_{17}H_{20}NaO$ $[M+Na]^+$ 263.1406, found 263.1408

(1*S*,5*R*)-1-((1*S*,5*R*,6*S*)-6-phenyl-3-oxabicyclo[3.1.0]hexan-1-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane 24f, (1*S*,5*R*)-1-((1*R*,5*S*,6*R*)-6-phenyl-3-

oxabicyclo[3.1.0]hexan-1-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane 24f', (3a*S*,5*R*,5a*S*)-5-phenyl-7-tosyl-3,3a,4,5,5a,6,7,8-octahydro-1*H*-furo[3,4-*e*]isoindole 25f and **(3a*R*,5*R*,5a*S*)-5-phenyl-7-tosyl-3,3a,4,5,5a,6,7,8-octahydro-1*H*-furo[3,4-*e*]isoindole 25f'** were isolated with 76 % yield (60.1 mg, 0.152 mmol) following the **GP-4** using **23f** (79 mg, 0.2 mmol) as reagent. **^{13}C NMR** ratio 75:25 for **24f**+**24f'**/**25f**+**25f'**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75 – 7.72 (m, 4H), 7.54 – 7.47 (m, 6H), 7.35 -7.20 (m, 18H), 7.13 – 7.05 (m, 8H), 6.92 – 6.85 (m, 10H), 4.30 (d, *J* = 13.1 Hz, 2H), 4.18 (d, *J* = 13.2 Hz, 2H), 3.98 – 3.80 (m, 6H), 3.74 – 3.64 (m, 4H), 3.52 (d, *J* = 8.1 Hz, 1H), 3.35 (dd, *J* = 9.0, 3.0 Hz, 2H), 3.27 – 3.21 (m, 1H), 3.18 – 3.11 (m, 3H), 3.03 (dd, *J* = 9.6, 3.8 Hz, 1H), 2.88 (d, *J* = 9.6 Hz, 1H), 2.74 – 2.67 (m, 3H), 2.51 (s, 6H), 2.43 (s, 6H), 2.19 (d, *J* = 4.3 Hz, 2H), 2.10 – 2.04 (m, 2H), 1.94 (dd, *J* = 8.8, 3.5 Hz, 1H), 1.83 (dd, *J* = 4.4, 2.9 Hz, 2H), 1.76 – 1.70 (m, 2H), 1.54 – 1.42 (m, 1H), 1.10 (dt, *J* = 8.2, 4.1 Hz, 1H), 0.94 – 0.89 (m, 1H), 0.66 (t, *J* = 4.5 Hz, 1H), 0.48 – 0.39 (m, 2H), 0.12 (t, *J* = 5.0 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.8 (Cq), 143.6 (Cq), 143.6 (Cq), 143.5 (Cq), 143.4 (Cq), 143.1 (Cq), 136.8 (Cq), 136.0 (Cq), 134.9 (2Cq), 134.0 (Cq), 133.8 (Cq), 133.6 (Cq), 132.9 (Cq), 132.2 (2Cq), 129.7 (CH), 129.5 (2CH), 129.5 (2CH), 128.7 (2CH), 128.7 (2CH), 128.6 (2CH), 128.4 (2CH), 128.1 (2CH), 127.7 (2CH), 127.4 (3CH), 127.2 (2CH), 127.0 (2CH), 126.8 (CH), 126.7 (CH), 126.5 (2CH), 126.3 (CH), 126.2 (CH), 126.1 (2CH), 125.7 (2CH), 73.7 (CH_2), 73.4 (CH_2), 73.1 (CH_2), 72.7 (CH_2), 70.0 (CH_2), 69.8 (CH_2), 68.8 (CH_2), 67.6 (CH_2), 53.6 (CH_2), 52.2 (CH_2), 52.2 (CH_2), 51.6 (CH_2), 50.1 (CH_2), 48.7 (CH_2), 48.6 (CH_2), 48.5 (CH_2), 47.7 (CH), 45.1 (CH), 43.2 ($2CH_3$), 42.7 (CH), 41.4 (CH), 37.3 (CH), 37.2 (Cq), 37.0 (Cq), 33.2 (CH_2), 31.5 (CH_2), 29.9 (CH), 29.6 (CH), 29.3 (CH), 26.6 (CH), 25.9 (CH), 25.5 (Cq), 24.9 (Cq), 23.8 (CH), 21.5 ($2CH_3$), 21.5 ($2CH_3$), 20.1 (CH), 15.7 (CH_2), 11.3 (CH_2). **HRMS** cald for $C_{23}H_{25}NaO_3S$ $[M+Na]^+$ 418.1447, found 418.1446.

(1*R*,1'*S*,5*R*,5'*R*,6'*S*)-6,6-dimethyl-6'-phenyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24g and **(1*R*,1'*R*,5*R*,5'*S*,6'*R*)-6,6-dimethyl-6'-phenyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24g'** were isolated with 61 % yield (33 mg, 0.12 mmol) following the **GP-4** using **23g** (54 mg, 0.2 mmol) as reagent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 7H), 7.12 – 7.09 (m, 3H), 4.09 (d, *J* = 8.5 Hz, 2H), 4.04 – 4.01 (m, 3H), 3.94 – 3.89 (m, 4H), 3.69 – 3.63 (m, 6H), 3.46 (d, *J* = 8.2 Hz, 1H), 2.77 (dd, *J* = 8.2, 3.7 Hz, 1H), 2.25 – 2.08 (m, 4H), 1.21 (s, 7H), 1.05 (s, 3H), 0.96 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.0 (Cq), 136.5 (Cq), 128.8 (CH), 128.1 (4CH), 127.7 (4CH), 126.0 (CH), 74.6 (CH_2), 74.1 (CH_2), 72.8 (Cq), 71.2 (CH_2), 70.2 ($2CH_2$), 69.4 (Cq), 68.4 ($2CH_2$), 67.5 (CH_2), 37.2 (Cq), 36.8 (Cq), 36.6 (CH), 34.5 (Cq), 34.1 (Cq), 32.0 (CH), 29.8 (CH), 29.6 (CH), 28.5 (CH), 24.0 (CH_3), 22.2 (CH_3) 21.0 (CH), 14.4 (CH_3), 13.5 (CH_3). **HRMS** cald for $C_{18}H_{22}NaO_2$ $[M+Na]^+$ 293.1512, found 293.1513.

(3a*S*,5*S*,5a*S*)-4,4-dimethyl-5-phenyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 25g and **(3a*R*,5*S*,5a*S*)-4,4-dimethyl-5-phenyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 25g'** were isolated with 19 % yield (10 mg, 0.034 mmol) following the **GP-4** using **23g** (54 mg, 0.2 mmol) as reagent. **^{1}H NMR** (400 MHz,$CDCl_3$) δ 7.32 – 7.19 (m, 10H), 4.44 – 4.30 (m, 4H), 4.25 – 4.20 (m, 4H), 4.11 (t, *J* = 7.6 Hz, 1H), 3.99 (q, *J* = 7.6 Hz, 2H), 3.87 – 3.84 (m, 1H), 3.50 – 3.39 (m, 2H), 3.29 – 3.09 (m, 4H), 2.72 (brs, 1H), 2.58 (brs, 1H), 2.45 – 2.39 (m, 1H), 2.18 (d, *J* = 9.9 Hz, 1H), 0.97 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H), 0.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3 (Cq), 139.2 (2Cq), 132.2 (Cq), 129.5 (Cq), 129.0 (2CH), 128.0 (4CH), 127.9 (CH), 126.9 (2CH), 126.6 (2CH), 73.6 (CH_2), 72.9 (CH_2), 69.6 (CH_2), 69.0 (CH_2), 68.7 (CH_2), 68.1 (CH_2), 67.8 (CH_2), 67.5 (CH_2), 54.2 (CH), 54.0 (CH), 52.5 (CH), 50.9 (CH), 43.5 (CH), 42.5 (CH), 35.3 (Cq), 34.8 (Cq), 28.0 (CH_3),

25.6 (CH_3), 25.2 (CH_3), 15.7 (CH_3). **HRMS** cald for $C_{18}H_{22}KO_2$ $[M+K]^+$ 309.1251, found 309.1250.

(2a*S*,2a^1*R*,2b*R*,5a*R*)-2a-((1*S*,5*R*,6*S*)-6-phenyl-3-oxabicyclo[3.1.0]hexan-1-yl)octahydrocyclopropa[*cd*]benzofuran 24h was isolated with 24 % yield (13.4 mg, 0.047 mmol) following the **GP-4** using **23h** (56 mg, 0.2 mmol) as reagent. **^{1}H NMR** (600 MHz, $CDCl_3$) δ7.31 – 7.27 (m, 2H), 7.20 – 7.17 (m, 3H), 3.95 (d, *J* = 8.3 Hz, 1H), 3.91 (d, *J* = 8.2 Hz, 1H), 3.88 – 3.86 (m, 1H), 3.82 – 3.79 (m, 2H), 3.76 (d, *J* = 8.0 Hz, 1H), 3.72 (d, *J* = 8.2 Hz, 1H), 2.20 (d, *J* = 4.5 Hz, 1H), 1.80 (dd, *J* = 4.5, 2.9 Hz, 1H), 1.62 – 1.56 (m, 1H), 1.50 – 1.39 (m, 2H), 1.31 – 1.16 (m, 4H), 0.89 – 0.85 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.2 (Cq), 128.9 (2CH), 128.1 (2CH), 126.1 (CH), 74.6 (CH), 74.2 (CH_2), 70.8 (CH_2), 70.2 (CH_2), 37.3 (Cq), 31.7 (Cq), 29.4 (CH), 27.1 (CH), 26.4 (CH), 25.6 (CH_2), 19.6 (CH), 17.3 (CH_2), 15.2 (CH_2). **HRMS** cald for $C_{19}H_{22}NaO_2$ $[M+Na]^+$ 305.1512, found 309.1514.

(2a*S*,2a^1*R*,2b*R*,5a*R*)-2a-((1*R*,5*S*,6*R*)-6-phenyl-3-oxabicyclo[3.1.0]hexan-1-yl)octahydrocyclopropa[*cd*]benzofuran 24h' was isolated with 24 % yield (13.4 mg, 0.047 mmol) following the **GP-4** using **23h** (56 mg, 0.2 mmol) as reagent. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 3H), 7.12 – 7.11 (m, 2H), 4.39 (dd, *J* = 5.1, 2.6 Hz, 1H), 4.09 (d, *J* = 8.3 Hz, 1H), 3.92 (d, *J* = 8.2 Hz, 1H), 3.77 - 3.75 (m, 2H), 3.70 (d, *J* = 8.6 Hz, 1H), 3.40 (d, *J* = 8.6 Hz, 1H), 2.20 (d, *J* = 4.3 Hz, 1H), 1.88 (dd, *J* = 4.4, 2.9 Hz, 1H), 1.56 – 1.50 (m, 2H), 1.42 – 1.38 (m, 1H), 1.30 – 1.24 (m, 2H), 1.18 – 1.13 (m, 1H), 0.91 – 0.84 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.7 (Cq), 128.5 (2CH), 128.0 (2CH), 125.9 (CH), 75.4 (CH), 73.0 (CH_2), 71.2 (CH_2), 70.1 (CH_2), 39.0 (Cq), 32.7 (Cq), 30.0 (CH), 26.5 (CH), 26.5 (CH_2), 23.9 (CH), 23.4 (CH), 16.5 (CH_2), 15.2 (CH_2). **HRMS** cald for $C_{19}H_{22}NaO_2$ [M+Na]+ 305.1512, found 309.1515.

(2a*S*,2a^1*R*,2b*R*,5a*R*)-2a-((1*S*,5*R*,6*S*)-6-(3-(trifluoromethyl)phenyl)-3-oxabicyclo[3.1.0]hexan-1-yl)octahydrocyclopropa[*cd*]benzofuran 24i was isolated with 21 % yield (14.3 mg, 0.04 mmol) following the **GP-4** using **23i** (70 mg, 0.2 mmol) as reagent. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 – 7.44 (m, 1H), 7.41 – 7.40 (m, 3H), 3.95 (d, *J* = 8.4 Hz, 1H), 3.91 – 3.89 (m, 2H), 3.80 (dd, *J* = 8.3, 2.9 Hz, 1H), 3.76 (d, *J* = 8.2 Hz, 1H), 3.73 – 3.71 (m, 2H), 2.22 (d, *J* = 4.4 Hz, 1H), 1.85 (dd, *J* = 4.4, 2.9 Hz, 1H), 1.60 – 1.54 (m, 1H), 1.50 – 1.45 (m, 1H), 1.44 – 1.38 (m, 1H), 1.31 – 1.16 (m, 4H), 0.87 – 0.83 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.6 (Cq), 132.7 (CH), 130.6 (q, *J* = 32.0 Hz, Cq), 128.6 (CH), 125.2 (q, *J* = 3.3 Hz, CH), 124.3 (q, *J* = 274.7 Hz, CF_3), 122.9 (q, *J* = 3.6 Hz, CH), 74.7 (CH_2), 74.2 (CH), 70.9 (CH_2), 70.2 (CH_2), 38.0 (Cq), 31.6 (Cq), 29.1 (CH_2), 27.7 (CH), 26.8 (CH), 25.8 (CH_2), 20.0 (CH), 17.2 (CH_2), 15.3 (CH_2). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.5. **HRMS** cald for $C_{20}H_{21}F_3NaO_2$ $[M+Na]^+$ 373.1386, found 373.1387.

(2a*S*,2a^1*R*,2b*R*,5a*R*)-2a-((1*R*,5*S*,6*R*)-6-(3-(trifluoromethyl)phenyl)-3-oxabicyclo[3.1.0]hexan-1-yl)octahydrocyclopropa[*cd*]benzofuran 24i' and **(2a*R*,2a^1*R*,5a*S*,6*R*,6a*S*)-6-(3-(trifluoromethyl)phenyl)-2a,2a^1,3,4,5,5a,6,6a,7,9-decahydro-1*H*-naphtho[8,1-*bc*:2,3-*c'*]difuran 25i'** were isolated with 30 % yield (21.3 mg, 0.061 mmol) following the **GP-4** using **23i** (70 mg, 0.2 mmol) as reagent. **^{1}H NMR** ratio 1 : 0.40 for **24i**' : **25i'**. **24i'** Major : **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.52 – 7.32 (m, 4H), 4.43 – 4.41 (m, 1H), 4.36 – 4.36 (m, 1H), 4.13 (d, J = 8.4 Hz, 1H), 3.95 (d, *J* = 8.3 Hz, 1H), 3.79 – 3.77 (m, 1H), 3.80 (d, *J* = 8.5 Hz, 1H), 3.72 (d, *J* = 8.6 Hz, 1H), 3.38 (d, *J* = 8.6 Hz, 1H), 2.27 (d, *J* = 4.3 Hz, 1H), 1.94 (dd, *J* = 4.2, 3.0 Hz, 1H), 1.59 (dd, *J* = 8.6, 4.8 Hz, 1H), 1.44 – 1.38 (m, 1H), 1.33 - 1.28 (m, 2H), 1.20 - 1.16 (m, 1H), 0.91 (td, *J* = 8.4, 4.5 Hz, 1H), 0.81 (ddt, *J* = 14.1, 9.4, 4.9 Hz, 1H). **^{13}C NMR**

(151 MHz, $CDCl_3$) δ 139.1 (Cq), 132.3 (CH), 130.3 (q, *J* = 23.7 Hz, Cq), 128.5 (CH), 124.9 (q, *J* = 3.8 Hz, CH), 124.2 (q, *J* = 272.3 Hz, CF_3), 122.8 (q, *J* = 3.6 Hz, CH), 75.4 (CH), 72.9 (CH_2), 70.8 (CH_2), 69.9 (CH_2), 39.3 (Cq), 32.3 (Cq), 29.6 (CH_2), 26.8 (CH), 26.2 (CH), 23.8 (CH_2), 23.3 (CH), 16.5 (CH_2), 14.7 (CH_2). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.4. **25i'** minor : **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.52 – 7.32 (m, 4H), 4.44 - 4.41 (m, 1H), 4.33 (brs, 1H), 4.18 (t, *J* = 7.9 Hz, 1H), 4.11 – 4.09 (m, 1H), 4.06 – 4.02 (m, 1H), 3.29 (dd, *J* = 10.6, 7.7 Hz, 1H), 3.05 – 3.02 (m, 1H), 2.88 – 2.87 (m, 1H), 2.15 – 2.12 (m, 1H), 1.76 – 1.66 (m, 2H), 1.56 – 1.48 (m, 2H), 1.44 – 1.38 (m, 2H), 1.33 - 1.28 (m, 1H), 0.61 – 0.55 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.8 (2Cq), 135.9 (CH), 132.7 (CH), 130.3 (q, *J* = 23.7 Hz, Cq), 126.9 (Cq), 124.2 (q, *J* = 272.3 Hz, CF_3), 126.0 (m, CH), 123.3 (q, *J* = 3.7 Hz, CH), 76.8 (CH_2), 68.1 (CH_2), 68.8 (CH), 72.1 (CH_2), 45.9 (CH), 42.4 (CH), 39.0 (CH), 38.4 (CH), 26.8 (CH_2), 24.7 (CH_2), 20.4 (CH_2). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.3. **HRMS** cald for $C_{20}H_{21}F_3KO_2$ [M+K]+ 389.1125, found 389.1126.

(2a*S*,2a^{1}*S*,5a*R*,6*R*,6a*S*)-6-(3-(trifluoromethyl)phenyl)-2a,2a^{1},3,4,5,5a,6,6a,7,9-decahydro-1*H*-naphtho[8,1-*bc*:2,3-*c'*]difuran 25i was isolated with 10 % yield (7 mg, 0.02 mmol) following the **GP-4** using **23i** (70 mg, 0.2 mmol) as reagent. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 – 7.50 (m, 2H), 7.47 – 7.45 (m, 2H), 4.45 – 4.41 (m, 2H), 4.28 – 4.22 (m, 3H), 4.12 – 4.09 (m, 1H), 3.24 – 3.21 (m, 2H), 3.06 (brs, 1H), 2.83 (dd, *J* = 10.6, 2.9 Hz, 1H), 2.22 (dtd, *J* = 11.9, 5.3, 3.2 Hz, 1H), 1.77 – 1.74 (m, 1H), 1.65 – 1.62 (m, 1H), 1.20 – 1.23 (m, 1H), 1.09 – 1.01 (m, 2H), 1.00 – 0.92 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.2 (Cq), 130.8 (CH), 128.9 (CH), 128.2 (Cq), 127.8 (Cq), 124.3 (CH), 124.1 (q, *J* = 272.0 Hz, CF_3), 123.6 (CH), 78.1 (CH), 72.5 (CH_2), 67.5 (CH_2), 65.8 (CH_2), 47.0 (CH), 45.9 (CH), 40.5 (CH), 40.0 (CH), 28.2 (CH_2),

21.8 (CH_2), 21.3 (CH_2). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.43. **HRMS** cald for $C_{20}H_{21}F_3KO_2$ [M+K]+ 389.1125, found 389.1124.

(1*S*,1'*S*,5*R*,5'*R*,6*S*)-2,2-dimethyl-6-phenyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24j, (1*R*,1'*S*,5*S*,5'*R*,6*R*)-2,2-dimethyl-6-phenyl-3,3'-dioxa-1,1'-bi(bicyclo[3.1.0]hexane) 24j', (3a*S*,4*R*,5a*S*)-1,1-dimethyl-4-phenyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 25j and **(3a*S*,4*R*,5a*R*)-1,1-dimethyl-4-phenyl-1,3,3a,4,5,5a,6,8-octahydrobenzo[1,2-*c*:3,4-*c'*]difuran 25j'** were isolated with 64 % yield (34.6 mg, 0.13 mmol) following the **GP-4** using **23j** (54 mg, 0.2 mmol) as reagent. **^{13}C NMR** ratio 70:30/ for **24j**+**24j'**:**25j**+**25j'**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.17 (m, 20H), 4.53 – 4.36 (m, 2H), 4.18 (q, *J* = 7.7 Hz, 1H), 3.97 – 3.84 (m, 6H), 3.74 (d, *J* = 7.7 Hz, 1H), 3.71 (d, *J* = 8.1 Hz, 1H), 3.64 (d, *J* = 7.6 Hz, 3H), 3.49 (d, *J* = 8.1 Hz, 1H), 3.44 – 3.24 (m, 4H), 2.97 – 2.82 (m, 2H), 2.67 – 2.60 (m, 1H), 2.44 – 2.43 (m, 2H), 2.40 – 2.33 (m, 3H), 2.13 (ddd, *J* = 12.3, 5.2, 2.4 Hz, 1H), 2.02 (dd, *J* = 4.0, 2.3 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.81 – 1.75 (m, 3H), 1.62 – 1.51 (m, 2H), 1.46 (s, 3H), 1.40 (s, 3H), 1.38 – 1.35 (m, 15H), 1.32 (s, 3H), 1.20 – 1.16 (m, 1H), 0.81 (ddd, *J* = 7.7, 4.5, 2.8 Hz, 2H), 0.62 (dd, *J* = 8.0, 4.5 Hz, 2H), 0.52 (t, *J* = 4.6 Hz, 2H), 0.38 – 0.35 (m, 1H), 0.14 (t, *J* = 4.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.7 (Cq), 144.4 (Cq), 140.3 (Cq), 138.2 (Cq), 137.7 (2Cq), 137.0 (2Cq), 129.9 (3CH), 129.0 (2CH), 128.7 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.1 (3CH), 128.0 (2CH), 127.3 (CH), 126.7 (CH), 126.7 (CH), 126.6 (CH), 126.2 (CH), 126.0 (CH), 83.8 (Cq), 83.6 (Cq), 81.4 (Cq), 80.3 (Cq), 72.8 (CH_2), 72.7 (CH_2), 71.5 (CH_2), 71.1 (CH_2), 70.4 (CH_2), 70.2 (CH_2), 69.5 (CH_2), 68.6 (CH_2), 67.0 (CH_2), 66.3 (CH_2), 66.2 (CH_2), 66.1 (CH_2), 48.5 (CH), 47.0 (CH), 44.9 (CH), 43.6 (CH), 43.0 (CH), 42.4 (CH), 41.3 (CH), 39.3 (CH), 32.1 (CH), 31.6 (Cq), 29.9 (CH_3), 29.3 (CH_3), 27.7 (Cq), 27.4 (CH), 27.2 (CH_3), 26.7 (CH_3), 26.4 (Cq), 25.9 (CH_2), 25.9 (CH), 25.7 (Cq), 24.7 (CH_3), 24.6

(CH_3), 24.4 (CH_3), 24.0 (CH_3), 23.8 (CH), 23.0 (CH_2), 13.5 (CH_2), 13.0 (CH_2). **HRMS** cald for $C_{18}H_{22}KO_2$ $[M+K]^+$ 309.1251, found 309.1252.

(1*S*,5*R*,6*S*)-6-phenyl-3-tosyl-1-((1*R*,2*R*,3*r*,4*S*,5*S*)-tricyclo[3.2.1.0^{2,4}]octan-3-yl)-3-azabicyclo[3.1.0]hexane 27 was isolated with 50 % yield (colourless oil, 42 mg, 0.1 mmol). Under argon a solution of *N*-cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (65 mg, 0.2 mmol, 1 eq.) in dry and degassed DMF (0.2 M, 1 mL) was added into a NMR tube charged with [Ir{dF(CF3)ppy}$_2$(dtbpy)]PF_6 (5.5 mg, 0.005 mmol, 2.5 mol%) followed by norbonene (376 mg, 4 mmol, 20 eq.) The reaction was irradiated at 45 °C for four days. The mixture was then concentrated and carefully purified by preparative TLC chromatography. (Hexane/Ethyl Acetate 8:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.26 – 7.22 (m, 2H), 7.17 – 7.14 (m, 1H), 7.09 (d, *J* = 7.1 Hz, 2H), 3.60 (dd, *J* = 16.3, 9.3 Hz, 2H), 3.13 (dd, *J* = 9.2, 3.9 Hz, 1H), 3.03 (d, *J* = 9.2 Hz, 1H), 2.45 (s, 3H), 2.08 (brs, 1H), 2.05 (d, *J* = 4.0 Hz, 1H), 1.77 (brs, 1H), 1.59 (t, *J* = 4.0 Hz, 1H), 1.28 – 1.26 (m, 2H), 1.10 – 1.02 (m, 2H), 0.63 (d, *J* = 10.6 Hz, 1H), 0.54 (brs, 1H), 0.43 (d, *J* = 10.6 Hz, 1H), 0.37 – 0.35 (m, 1H), 0.21 (d, *J* = 7.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4 (Cq), 137.4 (Cq), 133.8 (Cq), 129.6 (2CH), 128.9 (2CH), 127.8 (2CH), 127.4 (2CH), 125.9 (CH), 54.0 (CH_2), 50.4 (CH_2), 35.7 (CH), 35.4 (CH), 34.0 (Cq), 29.9 (CH), 29.3 (CH_2), 29.2 (CH_2), 28.1 (CH_2), 25.7 (CH), 23.4 (CH), 21.6 (CH), 21.5 (CH), 11.3 (CH). **HRMS** cald for $C_{26}H_{30}NO_2S$ [M+H]+ 420.1992, found 420.1991.

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9 List of abbreviations

BQ – Benzoquinone

Ts - toluenesulfonyl

TMEDA - Tetramethylethylenediamine

DMF - Dimethylformamide

DCE - 1,2-Dichloroethene

DMAP - 4-Dimethylaminopyridine

ACN - Acetonitrile

ee - enantiomeric excess

DCM - Dichloromethane

THF - Tetrahydrofuran

BzOH - Benzoyl alcohol/Benzoic acid

DIAD - Diisopropyl azodicarboxylate

HOMO - highest occupied molecular orbita

LUMO - lowest unoccupied molecular orbital

TLC - Thin-layer chromatography

DDQ - 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

dppe - 1,2-Bis(diphenylphosphino)ethane

dppp - 1,3-Bis(diphenylphosphino)propane

dppf - 1,1'-Bis(diphenylphosphino)ferrocene

Davephos - 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl

Jonhphos - (2-Biphenyl)di-*tert*-butylphosphine

Tbutxphos - 2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl

MA – maleic acid

Dppb - 1,4-Bis(diphenylphosphino)butane

MS – mesyl

PMB – para methyl benzyl

Bn – benzyl

TBS - *tert*-Butyldimethylsilyl

Boc - Ter-Butilossicarbonile

Phen - Phenanthroline

Bpy - 2,2′-Bipyridyl

Ppy - 2-Phenylpyridine

Dttbbpy - 4,4′-Di-*tert*-butyl-2,2′-dipyridyl

SET – single electron transfer

ATRA - Atom-Transfer Radical Addition

CFL - Compact fluorescent lamp

DMSO - Dimethyl sulfoxide

LED - Light Emitting Diode

DBU - 1,8-Diazabicyclo(5.4.0)undec-7-ene

DMA - Dimethylaniline

DABCO - 1,4-Diazabicyclo[2.2.2]octane

EWG – Electron withdrawing group

EDG – Electron donating group

COD - 1,5-Cyclooctadiene

Dpephos - Bis[(2-diphenylphosphino)phenyl] ether,

Pd-PEPPSI-IPr - [1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride

HFIP - Hexafluoroisopropanol

Brettphos - 2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl

TBN - tert-Butyl nitrite

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