UNIVERSITÀ DI PARMA

UNIVERSITA' DEGLI STUDI DI PARMA

DOTTORATO DI RICERCA IN
Scienze Chimiche

CICLO XXXIV

Visible light promoted polycyclizations of enynes and enallenes

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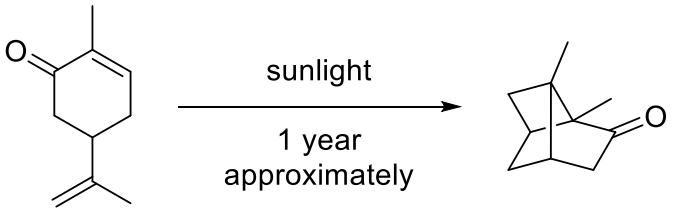
1 Introduction to visible-light catalysis

In a historical period in which the science attention is directed to the health of the earth, chemistry, the central science, is no exception. Among energetic sources, the sun light is undisputedly the more attractive. Sun light is the progenitor of almost all energetic sources on earth, from wind energy to hydroelectric power, passing through tides and fossil fuels. All organisms, directly or indirectly, depend on sun light. This basilary intuition is due to Jan Ingenhousz that, in 1779, discovered the essential role of light in process in which plants absorbed carbon dioxide and released oxygen, laying the groundwork for the understanding of photosynthesis. A hundred years were enough to the human genius to understand that the exploitation of this primary energetic source can be replaced.

Ciamician was the first to realize that organic reactions could be triggered by visible light and, in 1886, he published his work on the conversion of quinone into quinol by light[1]. In the beginning of the XX century, contemporarily to the advent of quantum mechanics that provided rigorous methods for understanding light-matter interactions, Ciamician and Paternò built the groundwork of modern photochemistry. The Ciamician contributions was evidenced by his discoveries on the photoreduction of many important classes of functional groups like ketones, aldehydes quinines and nitro-compounds. Also, his discoveries on 2+2 photocycloaddition, with the example of carvone, were remarkable (Scheme 1).



Scheme 1 2+2 photocycloaddition performed by Ciamician under solar radiation.

In 1909 Paternò and Chiffi exposed to sunlight for 104 days a solution of 2-methyl-2-butene and benzaldehyde obtaining corresponding 4-membered heterocyclic rings without fully understanding the structure of oxetane products and the reaction mechanism. The experiment was reproduced in 1954 by George Buchi that rationalized the mechanism and characterized the product[2]. For this reason, the reaction of Paternò was renamed Buchi-Paternò reaction. In the ensuing decades the use of light was restricted to materials chemistry with particular attention toward industrial transformation using cheap titanium dioxide[3–5]. From the beginning of this century the increasingly interest toward environmental problems led to development of potentially scalable methods for hydrogen production[6,7] and wastewater treatment[6,8].

In the last 10 years an exponential growth of photocatalysis applied to organic synthesis was observed[9–11]. Photocatalysis provided us a series of transformations unthinkable until few years ago thanks to the opportunity to access high energy intermediates selectively without affecting other functional groups.

1.1 Photoredox catalysis

The most extensively studied aspect of photocatalysis applied to organic synthesis involves single electron transfer (SET) processes. Either organic dyes[12] or transition metal complexes, based on ruthenium or iridium commonly but many others metal are subject to study[13,14], can be used as photoredox catalyst (Figure 1). The latter showed amphoteric redox properties that make them more versatile. This unique property of the excited state of transition metal catalyst is due to the open shell configuration that follow photon absorption. In addition, thanks to the large spin-orbit coupling constant of the heavy metal atom, transition metal catalysts easily can access long-lived excited triplet states.

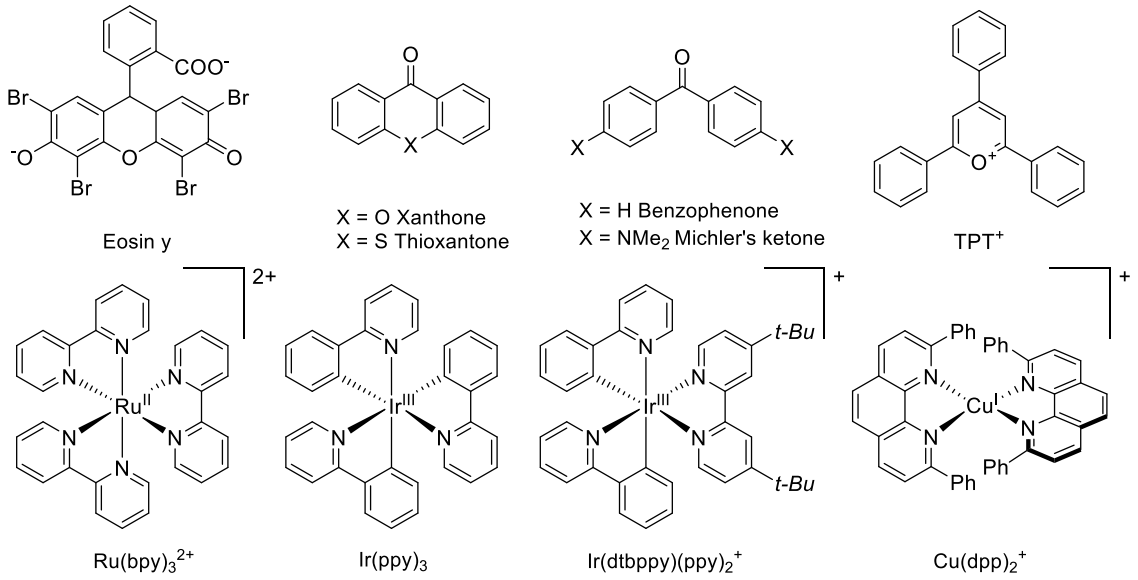
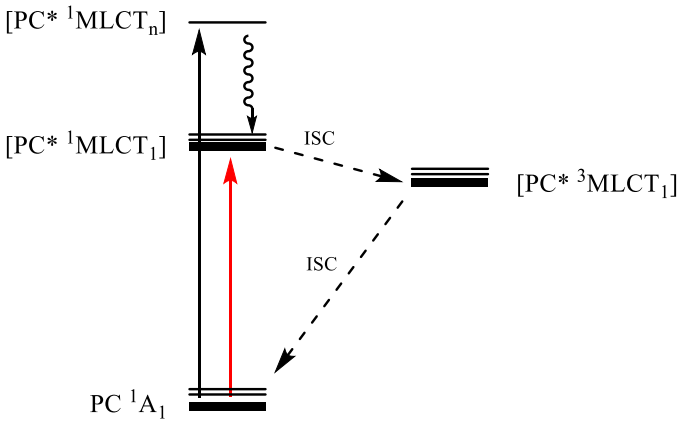


Figure 1 selected examples of commonly used photoredox catalysts.

As a result of absorption, the energy associated to the radiation is transferred to an electron in t_2g orbital that is promoted to π* ligand orbital through a process known as Metal to Ligand Charge Transfer (MLCT). Given the broad absorption range of Ir an Ru complexes, transition leads initially to various singlet excited states [PC* $^1MLCT_n$] that rapidly relax to the low energy spin-allowed state [PC* $^1MLCT_1$]. Intersystem crossing (ISC) converts [PC*



scheme 2 Simplified Jablonsky diagram of a generic metal-based photocatalyst.

$^1MLCT_1$] in long-lived triplet state [PC* $^3MLCT_1$] [9] (Scheme 2). Electronic configuration of the excited triplet state is the key for its ability to act as oxidant/reductant at the same time (Figure 2, b)), but also is responsible for the energy transfer (eT) process that will be described afterwards. The presence of an unpaired electron in the SOMO is the cause of reductant properties. Similarly, the gap in the $SOMO^{-1}$ make possible the oxidative process (Figure 2, a)). The driving force for the electron transfer process, in which photocatalyst can act as oxidant or reductant, can be estimated using Rehm-Weller equation:

$$\Delta G_{eT} = \mathrm{E}(D^+/D) - \mathrm{E}(\mathrm{A}/A^-) - \Delta E_{00}$$

Where the firsts two values correspond to the donor and acceptor ground state potentials respectively while the last value correspond to the energy gap between the excited state and the lowest vibrational state of the ground state of the photocatalyst[15]. Playing with the ligands structure makes possible the energy modulation of semi-occupied orbitals and, consequently, the fine tuning of redox potentials[16].

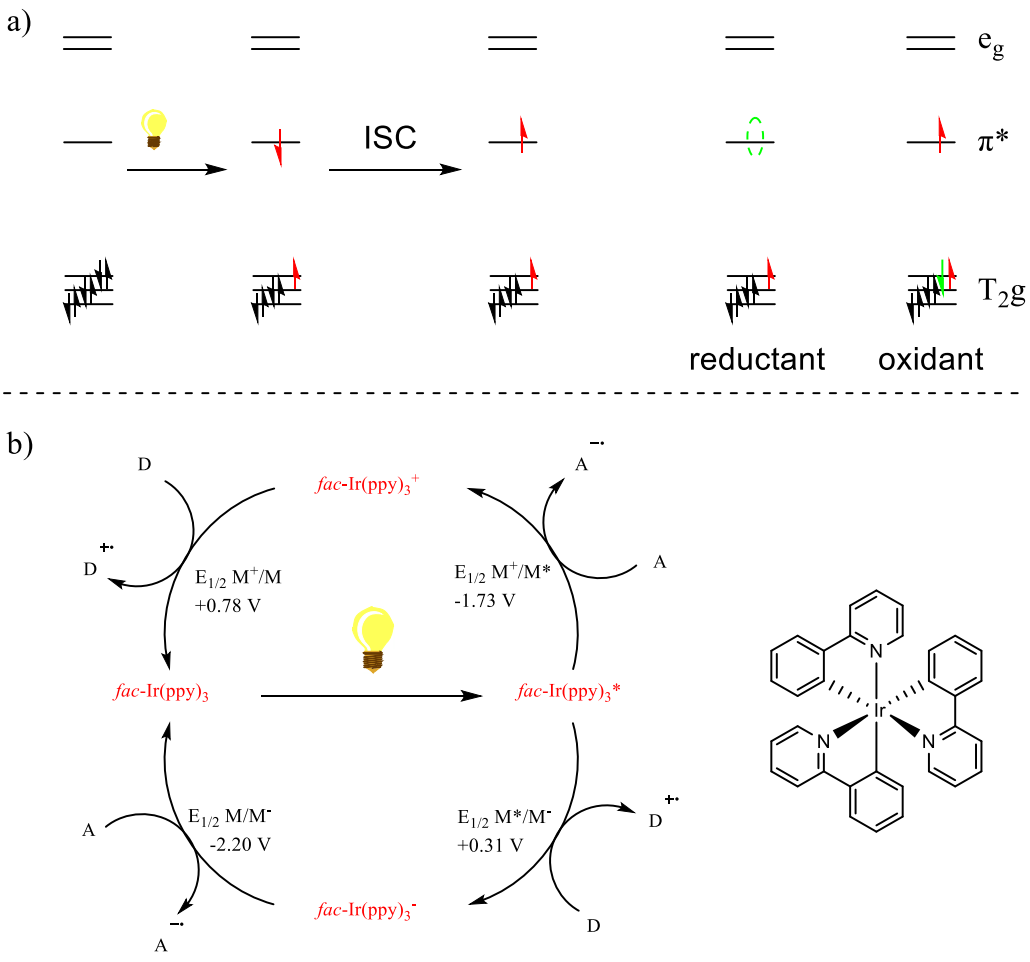
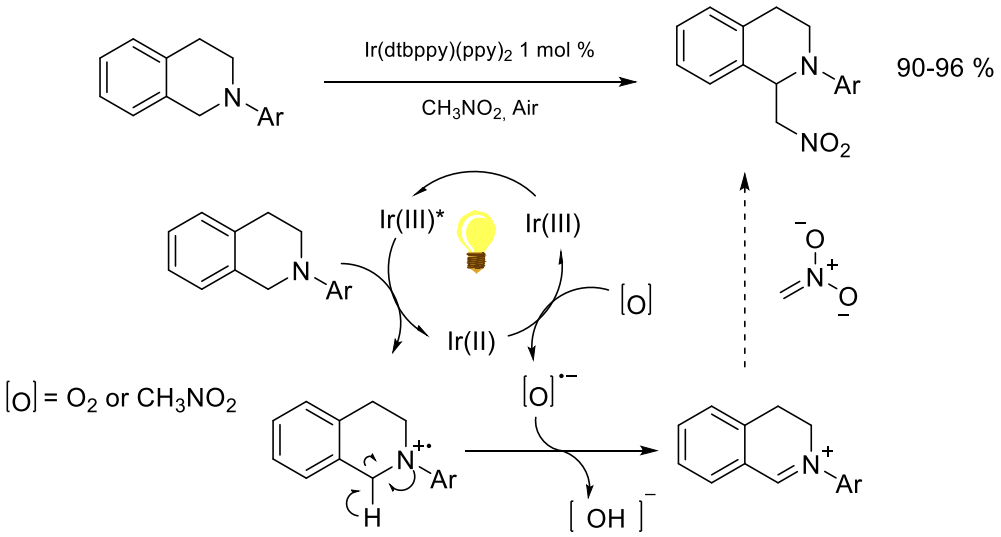


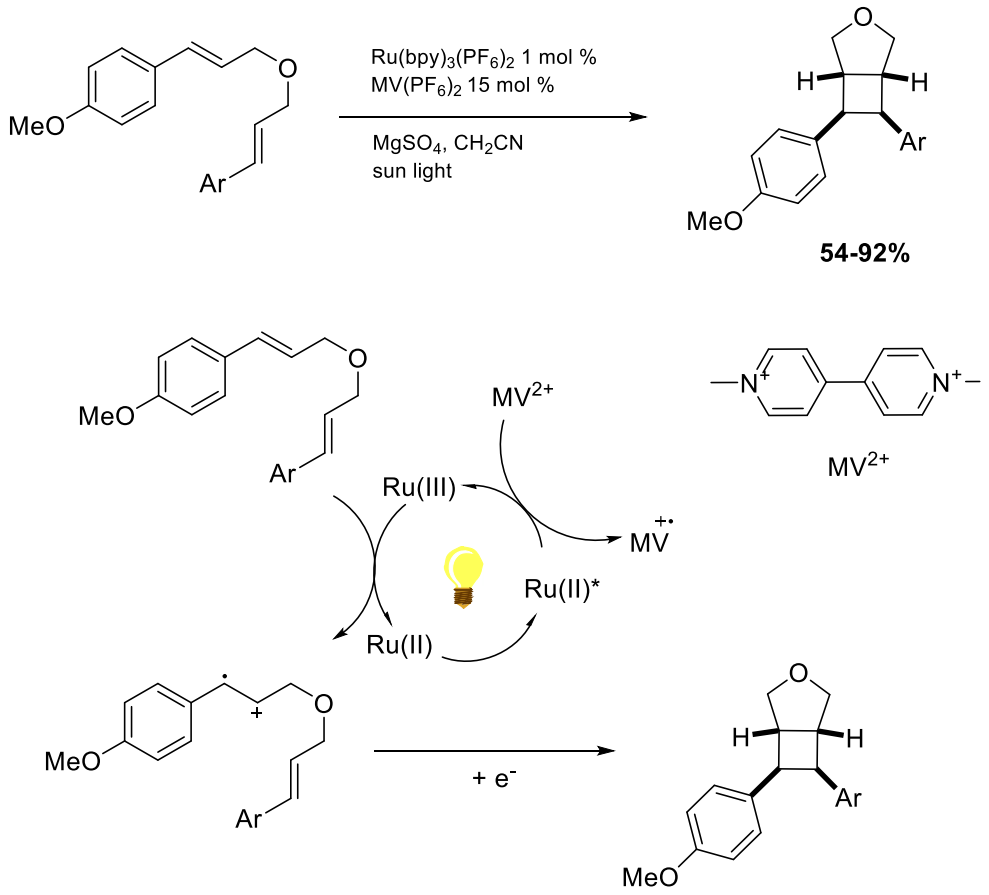
Figure 2 a) molecular orbital depiction of $Ir(ppy)_3$ b) oxidative and reductive quenching cycle of $Ir(ppy)_3$.

These redox properties were widely used in organic synthesis since the early 2000s[10,11]. The oxidation of electron-rich substrates paves the way to un uncredible number of transformations. Among these, the α-functionalization of amines is remarkable. Thanks to early work of Stevenson and co-workers that performed aza-Hanry reactions under photoredox catalysis in 2010[17], a general tool for these transformations was developed. Typically, the first oxidation of the amine provides a radical cation on the nitrogen atom that make relatively easy the hydrogen atom abstraction from the α-position. The resultant iminium ion undergoes nucleophilic addition delivering corresponded α-functionalized amines (Scheme 3).



Scheme 3 selected example of α-functionalization of arylamine *via* photoredox process.

The access to a stronger oxidant/reductant agent is possible. Using transition metal catalyst M^n, which have access to different range of oxidation states, and a sacrificial oxidizing/reducing agent, we can access to energic oxidant/reducing $M^{n\pm1}$ state, as we can see from the redox potential expressed in Figure 2 for $Ir(ppy)_3$. Using this strategy, Yoon and co-workers reported the intramolecular 2+2 cycloaddition of anetyl-cynnamil ether using Ru catalyst[18]. Methyl viologen (MV^{2+}) was used as sacrificial oxidizing agent. Upon SET from Ruthenium triplet state to methyl viologen salt, the resultant Ruthenium (III) species can oxidize anetyl fragment affording the corresponding radical cation intermediate. Sequential cyclization, reduction and ring-closure eventually provided the 3.2.0 product (Scheme 4).



Scheme 4 selected example of formal 2+2 cycloaddition triggered by reductive quenching of Ru(III) catalyst.

However, oxidation/reduction processes remained difficult for substrates whose redox potential, in absence of functionality, remain inaccessible without affect sensitive functional group. As evidenced by chloroarenes, unsubstituted styrene (+1.97V Vs SCE) and similar derivatives[19].

1.2 Energy transfer, fundamentals and application in organic synthesis

The access to excited state molecules paves the way for many organic transformations. However usually, the direct activation of commonly used building blocks in organic synthesis requires short-wave UV radiations, the use of which brings to light obvious safety considerations. The use of energetic UV radiation can also cause structural degradation of many functional groups. These considerations restrict the enforceability of this method.

The use of a sensitizer, which can be either a transition metal complex or an organic dye, that collects visible light energy transferring it to substrates via energy transfer (eT)[20], bypassed the above-mentioned issue. eT is a non-radiative process in which energy is transferred from excited state (donor D) to a ground state (acceptor A). However, a more rigorous definition is reported: "energy transfer is the photophysical process in which an excited state of one molecular entity (the donor D) is deactivated to a lower-lying state by transferring energy to a second molecular entity (the acceptor A), which is thereby raised to a higher energy state."[21]

A commonly observed mechanism for energy transfer process starts as always, with photon absorption by a sensitizer. Dipole variation caused by electronic oscillation in the excited donor induces a dipole moment thereby causes electronic oscillation in the ground state acceptor through electromagnetic interaction. This very efficient mechanism for energy transfer is known as Förster resonance energy transfer (FRET) and it is fundamental, for example, in the photosynthesis[22] (Figure 3, left). Unfortunately, it is unlikely that this theory, which efficiently explain eT between singlet states, can explain a triplet-triplet eT. This double transition, from triplet to singlet state in the donor and from singlet to triplet in the acceptor, would violate two times the Wigner's spin conservation rule.[21].

The most accredited mechanism with which triplet-triplet eT can be rationalized, without violating Wigner's spin conservation rules, was descripted by Dexter in 1953[23]. In essence, is a double electron transfer from SOMO of excited donor to LUMO of acceptor and from HOMO of acceptor to $SOMO^{-1}$ of the excited donor (Figure 3, right).

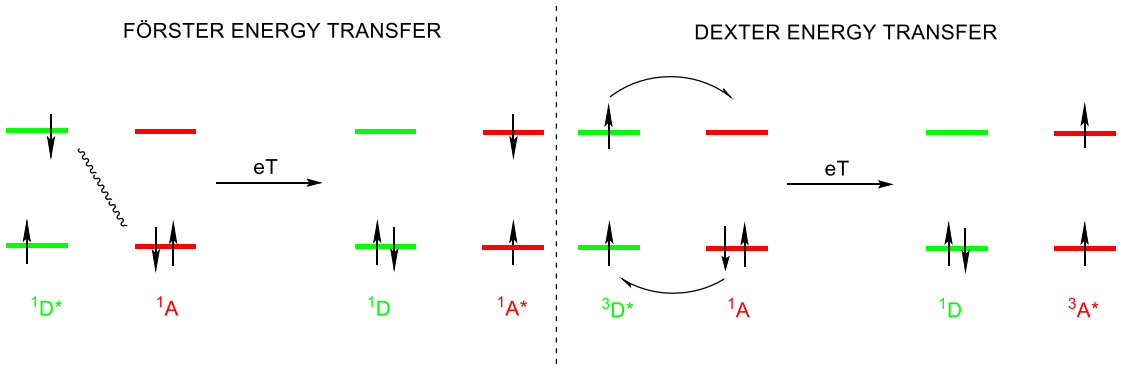
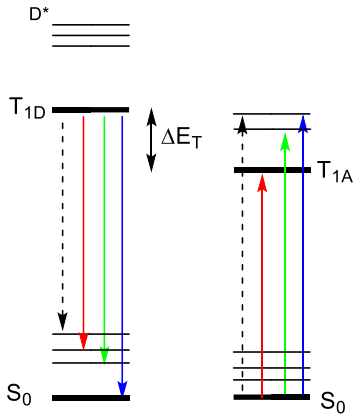


Figure 3 schematic description of Förster and dexter energy transfer.

The rate of Dexter energy transfer is affected by multiple factors.

$$k_{eT} = K\,J\,e^{\frac{2R_{DA}}{L}}$$

When K is a parameter related to orbital interactions between partners of eT, it is strongly correlated to steric repulsion. R_{DA}/L represent the physic distance between donor D and acceptor A, consequently the rate of eT decay exponentially with the distance as observed for SET processes. J is an overlap integral between donor emission spectrum (phosphorescence spectrum) and acceptor absorption spectrum (S_0 to T_1), and both are normalized (Scheme 5). This factor is directly correlated to the number of energy transfer events, hence with the actual rate of eT. The experimental determination of J can be extremely challenging because of the measure of the energy gap between the triplet and the singlet states is not trivial. A good approximation for J value can be obtained by the energy difference (ΔE_T) between triplet states of acceptor and donor respectively. If $\Delta E_T < 0$ the process is formally exergonic and many events occur, only limited by diffusion. If, on the contrary, $\Delta E_T > 0$ the process is formally endergonic and the only energy transfer events occur from rotational and vibrational excited state of T_1 donor whose population depends on thermal energy following the Boltzmann distribution.



Scheme 5 a simplified Jablonsky diagram in which coupled transition represent the overlap between emission and absorption spectrum.

$$J \propto e^{-\frac{\Delta E_T}{k_b T}}$$

Although application of this process to organic chemistry is still not widespread compared to SET, in the last years an increasingly number of publications in this field come out[24]. This process shows its potential in a myriad of applications. One of the first was *contra*-thermodynamic isomerization of *E*-olefins. Introduced for the first time by Hammond and co-worker in 1964 using stilbene as unsaturation[25], this approach offers a simple resolution to a problem old as the discovery of alkenes themselves. Testing several sensitizers, Hammond obtained an excess of *Z*-stilbene at the photo stationary state starting from pure *E*-stilbene. This was due to the energy of triplet state of *Z*-stilbene, which was different from *E*-stilbene, not matching with that of the sensitizer. Consequently, its conversion to *E*-stilbene was slower than that of the opposite process (Figure 4). In the ensuing decades, many styrenyl-alkene isomerization methods were delivered clarifying the reaction mechanism[26].

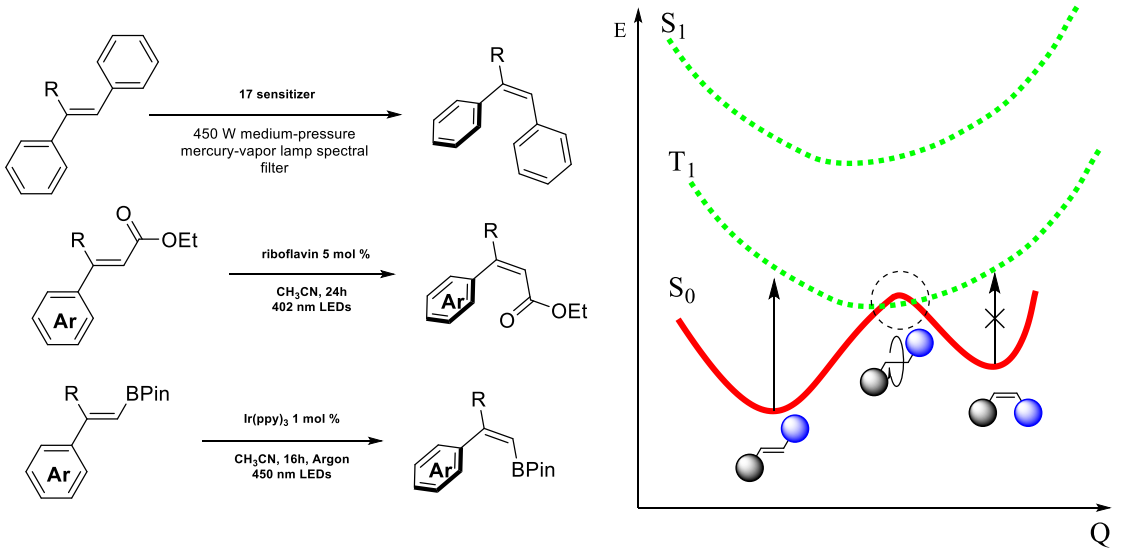
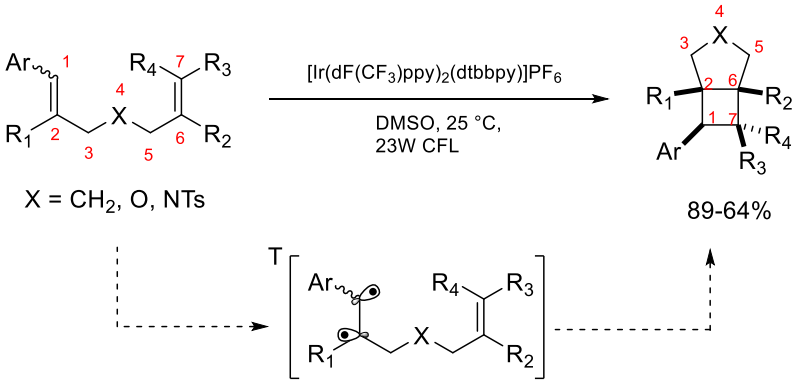


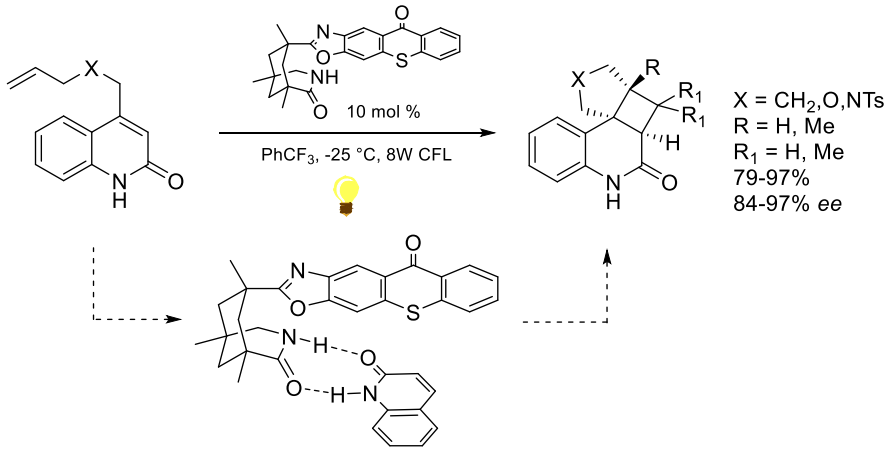
Figure 4 selected examples of contra-thermodynamic isomerization of styrenes.

Starting from 2010, activated triplet state of styryl fragment was extensively employed in cyclization reactions[27]. Seminal research in this field is due to Yoon and co-workers that in 2012 published an intramolecular 2+2 cycloaddition promoted by visible light[28]. In this example $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (E_T = 61.8 Kcal/mol) was employed for the activation of dienes ($E_T \approx$ 55.0 to 60.0 Kcal/mol). The energy transfer between PC donor and styrene arm acceptor afforded a diradical intermediate that undergoes a *5-exo-trig* cyclization in which a new σ-bond between C2 and C6 was formed. The instant recombination of radicals in positions 1 and 7 that followed the ISC afforded the 3.2.0 bicyclic structure (Scheme 6).



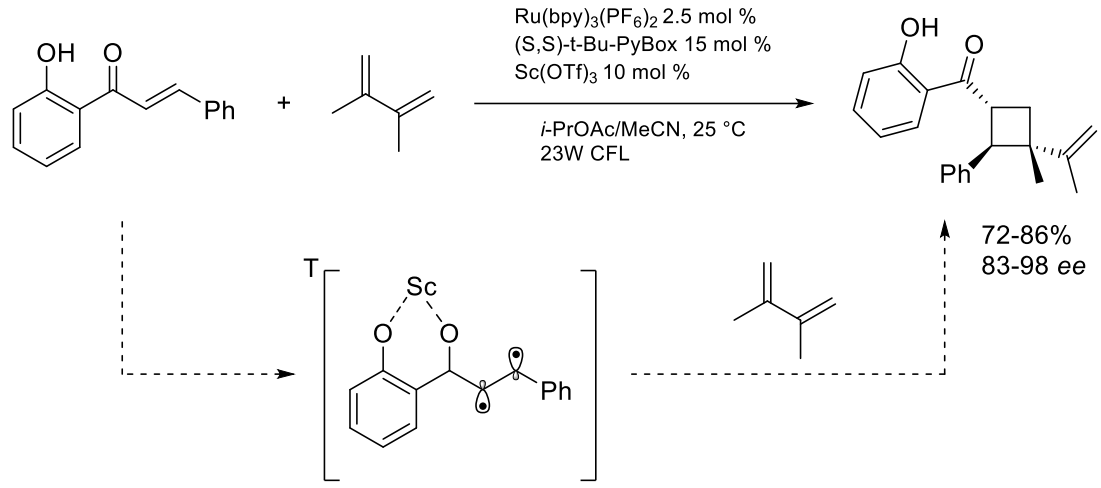
Scheme 6 Selected example of 2+2 cycloaddition triggered by eT.

Bach and co-workers reported in 2014 an enantioselective 2+2 cycloaddition using a chiral based thioxanthone sensitizer[29]. Prochiral quinolone approaches the catalyst from a preferential enantioface driven by hydrogen bonding between amide fragments. Irradiation of this complex promoted a highly efficient eT that triggered the intramolecular cyclization on the unshielded face delivering product with excellent enantioselectivity (Scheme 7).



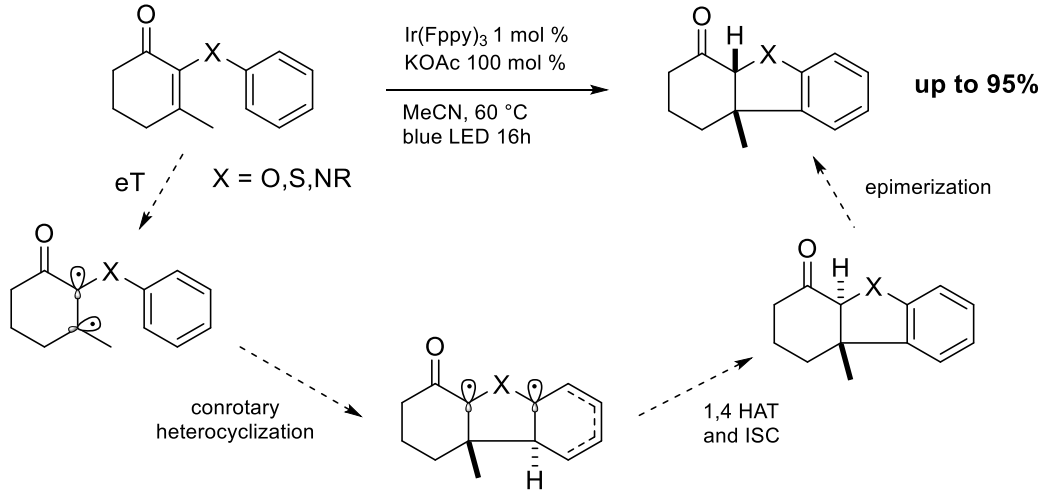
Scheme 7 selected example of organocatalyst employed in an enantioselective 2+2 photocycloaddition.

In 2016 Yoon and co-workers developed a fascinating 2+2 cycloaddition assisted by chiral Lewis acid[30]. The latter played a dual role. In addition to bringing chiral information, it contributed to lower the energy of substrate triplet state (E_T = 33.0 Kcal/mol for the complex) through the coordination to the cinnamic ketone (E_T = 55.0 Kcal/mol), making the process efficient using $Ru(bpy)_3(PF_6)_2$ (E_T = 49.0 Kcal/mol) (Scheme 8) despite its relative low triplet state.



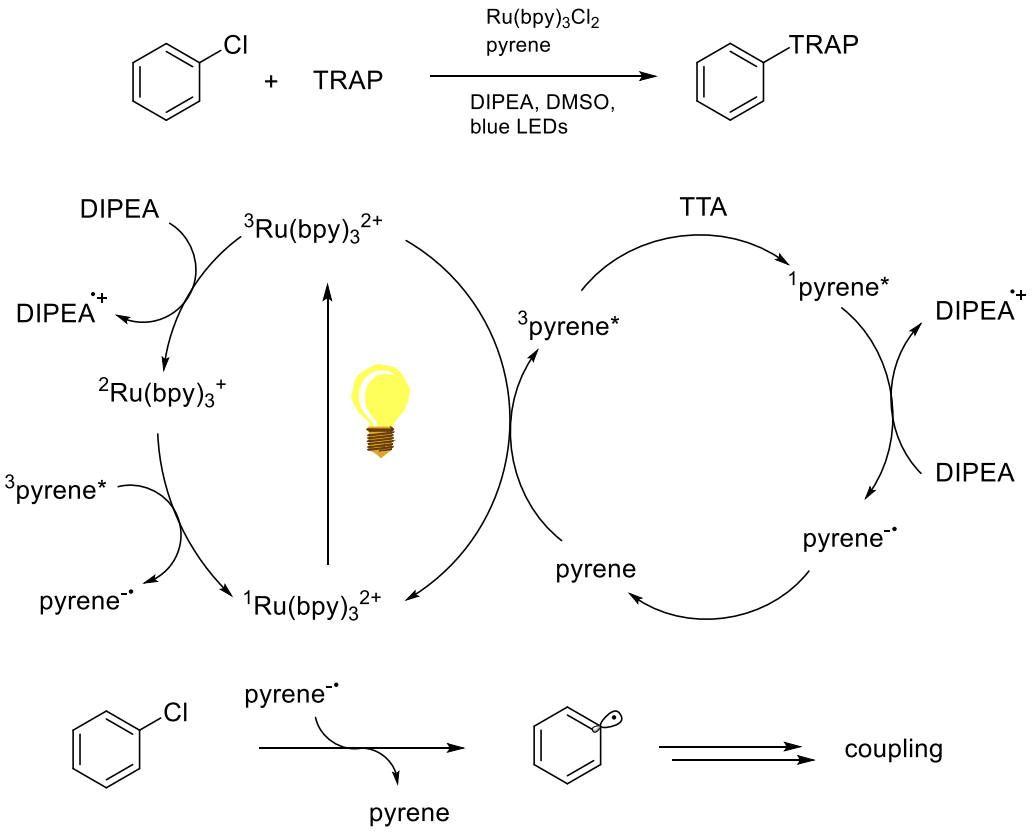
Scheme 8 selected example of enantioselective 2+2 photocycloaddition assisted by Lewis acid.

An evidence of the versatility of methods based on eT, Smith and co-workers reported the 6π heterocyclization of 2-aryloxyketones promoted by visible light[31]. In the proposed mechanism, Ir activated the substrate via eT, and the following conrotatory intramolecular cyclization (suggested by DFT calculation) afforded a tricyclic intermediate in its triplet state. Upon ISC, 1,4-HAT followed by epimerization delivered the corresponding product (Scheme 9).



Scheme 9 selected example of 6π heterocyclization promoted by eT.

Finally, a fascinating example was provided by König and co-workers that reported a tool for the challenging activation of EWGs substituted aryl chloride[32]. This method, in which a process of sensitization-initiated electron transfer (senIET) occurred, showed a simultaneous use of SET and eT to access a strongly reductant agent difficult to obtain under mild conditions. Polycyclic aromatic hydrocarbon radical anion species show a strongly reductant power. However, the corresponding neutral precursor does not absorb photon in the visible spectral window. To circumvent this issue, an appropriate sensitizer can be used. In the reported example, pyrene was activated via eT by the Ru catalyst, The new excited pyrene can be quenched by Ru coming from another cycle affording the corresponding radical anion or meet another triplet pyrene leading to an even more energetic singlet excited pyrene species through a process that is called triplet-triplet annihilation (TTA)[33,34]. The latter then accepts an electron from a secondary amine affording a radical anion. Both processes deliver strongly reductant agents that can easily reduce electron poor aryl chloride. The radical anion aryl chloride undergoes fragmentation delivering a phenyl radical that was subsequently trapped by opportune reagents (Scheme 10).



Scheme 10 selected example of aryl chloride activation using combination of SET and eT.

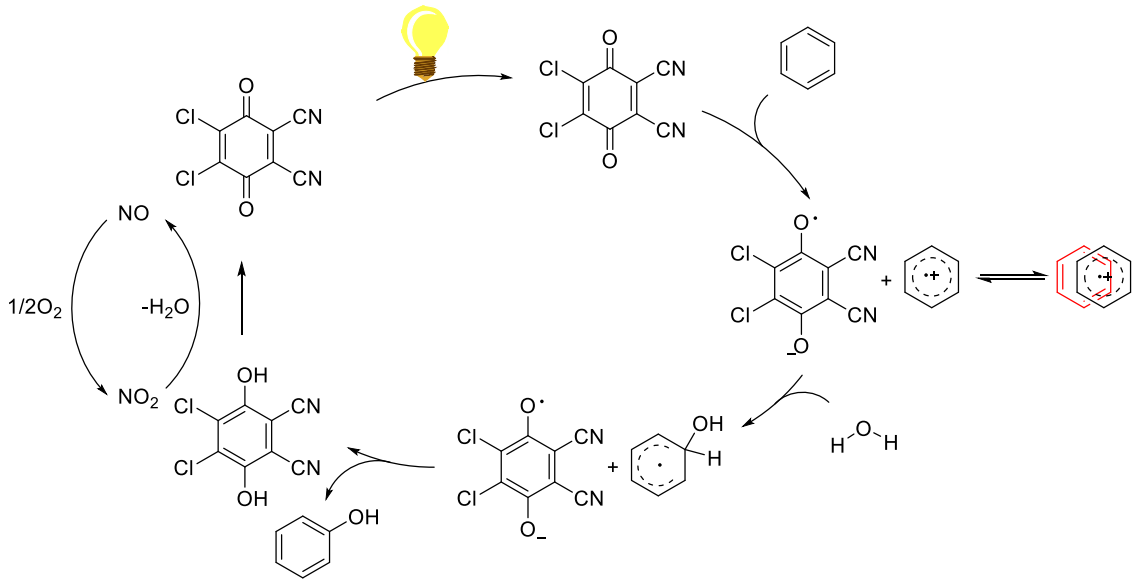
2 Two photons trigger Intermolecular polycyclization of enynes with alkenes

2.1 Introduction

Oxidation reactions are among the oldest phenomena observed by humans. Despite the curiosity aroused by these events, its understanding required centuries and, only in the last hundred years, thanks to the discoveries on the atomic structure, scientists began to realize the mechanism of these events. Electron transfers are involved in a myriad of biological processes and are very important in materials science. For these reasons, the control of oxidation pathways remains of crucial importance for the chemical sciences.

Recently, in the field of organic chemistry, the attention was focused on the feasibility to trigger fascinating transformations *via* controlled oxidation of substrates generating unstable radical cationic intermediate. Many progresses in this field came from photocatalysis. The possibility to access strongly oxidizing agent under mild condition is the main strength that makes it one of the most important emerging fields in organic synthesis. Transition metal photocatalysts were widely used as oxidating agents but their potential, also in the oxidized configuration, rarely exceeded +1.7 V versus SCE. Some organic dyes, on the contrary, can easily overcome this value.

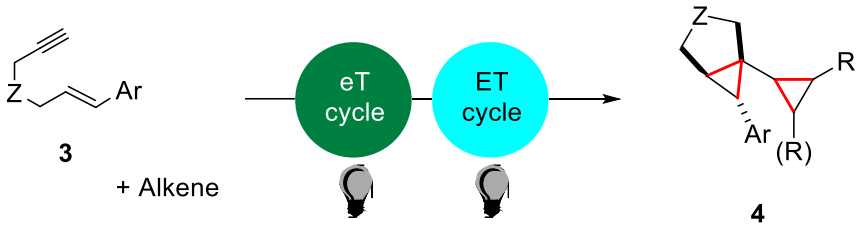
Fukuzumi and co-workers optimized a method for the direct oxidation of benzene to phenol taking advantages from the oxidizing power of excited DDQ[35]. The reaction began, as usual, with exergonic electron transfer from benzene (+2.48 V versus SCE) to the excited triplet state of DDQ (+3.18 V versus SCE). Just formed benzene radical cation generated a π-dimer with benzene which was in equilibrium with the monomeric cationic form. The latter undergoes water addition affording a radical hydroxyl adduct that was readily oxidized to phenol by semi reduced DDQ^-. $DDQH_2$ was oxidized by NO_2 produced by oxidation of NO with O_2 (scheme 11). It is worth noting that semi reduced DDQ^- would have greater tendency to reduce the benzene radical cation rather than oxidize the radical hydroxyl adduct. In such case, the reduction of benzene radical cation by DDQ^- occurred in the Marcus inverted region while the oxidation of radical phenol occurred in the Marcus top region. This means that the latter process in thermodynamically less favoured but much faster than the reduction of the benzene radical cation[36,37].



Scheme 11 Selected example of direct oxidation of benzene to phenol.

However, the use of this energic oxidant implies several problems. Many useful functional groups, including carboxylates, carbamides and same amides, were unable to tolerate this condition restricting the tool to very simple substrates. In addition, even some commonly used organic solvents were not inert under these conditions.

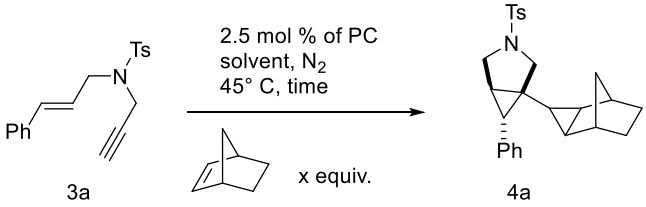
In a previously work published by our research group a conceptually complementary route for the activation of seemingly redox inert dienynes was reported. Instead of pushing the lever of redox potentials, the latters were activated through a sequential two-photon-promoted eT/ET process using photocatalysts that are able to induce both. The resulting cascade reaction afforded a mixture of tri- and tetracyclic fascinating scaffolds. Herein we reported the challenging extension from intra- to intermolecular pathway joined to important developments about the understanding of mechanism which rules this reaction (Scheme 12).



Scheme 12 intermolecular cascade via two photons promoted catalytic cycle.

2.2 Results and discussion

Combination of enyne **3a** and norbornene was selected to optimize reaction conditions (table 1). The substrate was dissolved in the solvent and photocatalyst (2.5 mol %) was added. The mixture was transferred in a 5 mm NMR tube, sealed with a rubber septum and degassed via freezing pump. The choose of an NMR tube as reaction vessel allows to obtain high surface/volume ratio, which was crucial for this reaction. The mixture was placed into a high-vacuum-grade silicone-oil bath, which was warmed at the desired temperature, and irradiation was ensured by a household 7W RGB LED strip (spectral window from 350 to 750 nm) (figure 6). Thanks to a rubber septum on the tube, samples were periodically taken to monitor the progress of the reaction by TLC.



Entry[a]	Solvent	Photocatalyst	Conc. of **3a** (M)	Yield of **4a** (%)[b]
1	DMF	PC1	0.4	31%
2	DMF	PC2	0.4	--
3	DMF	PC3	0.4	48%
4	DMF	PC4	0.4	52%
5	DMF	PC4	0.5	44%
6	DMF	PC4	0.2	36%
7[c]	DMF	PC4	0.4	42%
8	DMSO	PC4	0.4	41%
9	DMF/MeOH 3:1	PC4	0.4	49%
10	DMF/DCM 3:1	PC4	0.4	50%
11[d]	DMF	PC4	0.4	59%
12[e]	DMF	PC4	0.4	31%
13	DMF	PC5	0.4	--
14	DMF	PC6	0.4	--
15[f]	DMF	PC4	0.4	--

Table 1 a: reaction conditions, 0.2 mmol of 1a, 20 equiv. of norbornene, 2.5 mol% cat., dry and degassed solvent, into unstirred NMR tubes, warmed at 45 °C for 96 hours; b: ^{1}H NMR yield using 1,3,5-trimethoxy benzene as internal standard; c: for 72 hours; d: with 50 equiv. of norbornene; e: with 10 equiv. of norbornene; f: without irradiation.

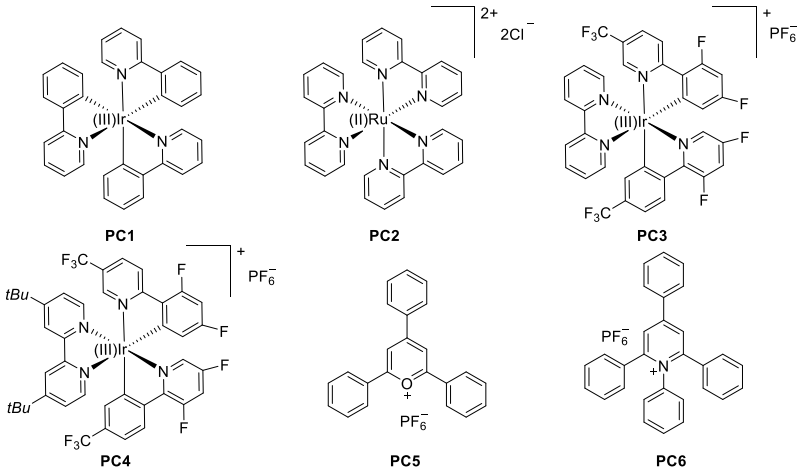


Figure 5 Photocatalyst employed in the optimization process.

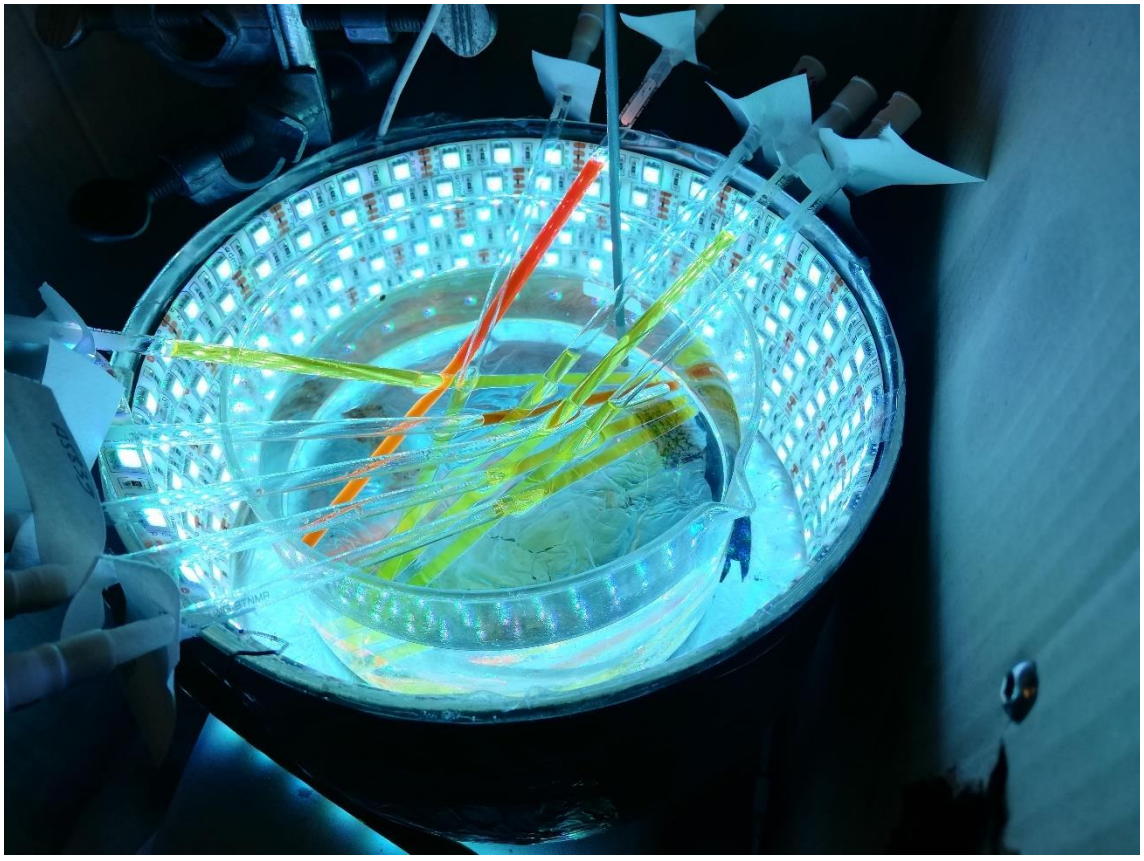
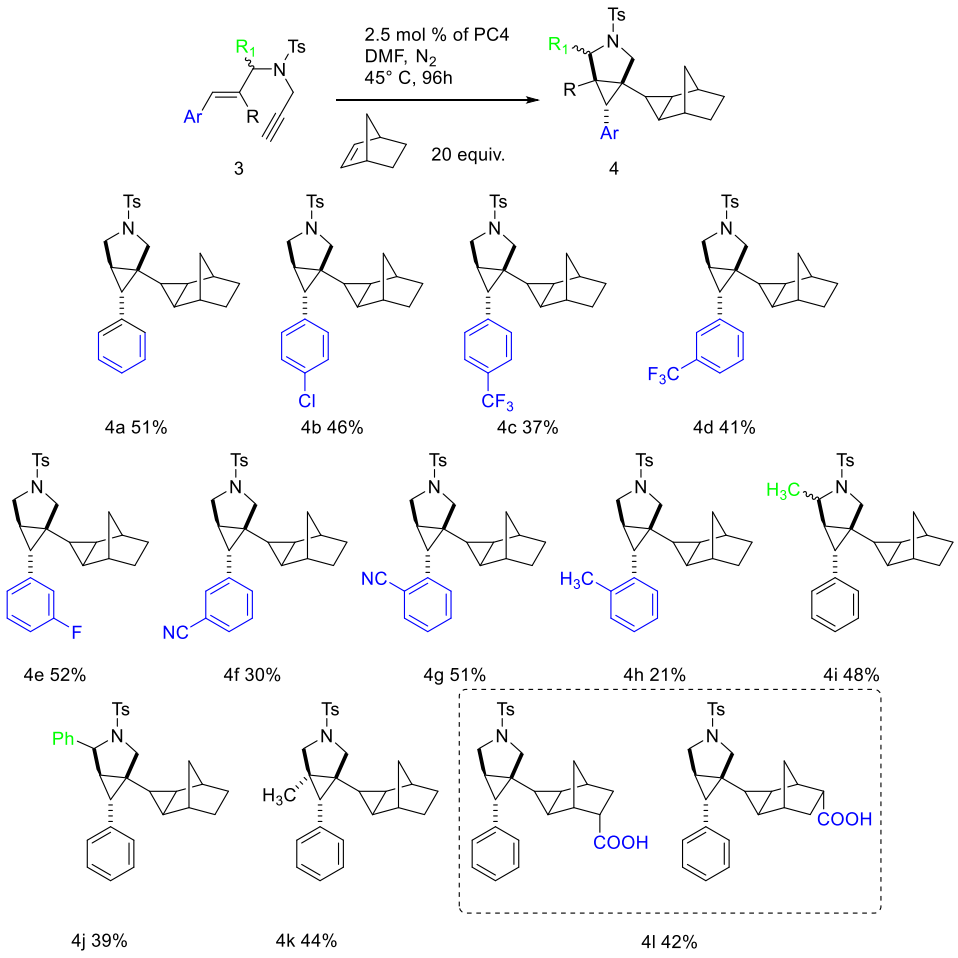


Figure 6 picture of reaction set-up

The use of $Ir(ppy)_3$ as catalyst delivered desired product **4a**, as a single isomer, in 31% yield (entry 1). Four days were required to observed full conversion of the starting material. Together with some decomposition of the reagent, mass balance could be accounted for by the presence of traces of the *Z*- isomer of the substrate, which is no longer prone to undergo activation under these conditions. The use of popular Ruthenium photocatalyst **PC2** did not induce any conversion of **3a** (entry 2) probably because of low energy of its triplet state (33.0 Kcal/mol) compared to styrenes (≈ 50-60 Kcal/mol). In addition, the redox potentials of PC2 doesn't match with enynes and alkenes here used. On the contrary, different Ir(III) photocatalyst proved able to trigger the desired polycyclization (entries 3-4) and best results were achieved using **PC4** (52% yield). The outcome benefits from an increase of enyne concentration with the best result achieved at 0.4 M. Performing the model experiment for a shorter period (72 hours, entry 7), led to partial recovery of **3a** and a slightly lower yield of **4a** (42%). A highly polar solvent was required by the sequence and the product formed in traces only in apolar media. Different solvents and their mixtures proved capable to induce the desired reaction (entries 8-9) and best results were achieved employing DMF. A similar outcome was observed using a DMF/DCM mixture (entry 10, 50%), likely because the latter can more readily solubilize the apolar norbornene, which is present in a molar excess. Further increase of the latter can benefit the yield of **4a** (entry 11, 59%), but this modification was not further tested for practical reasons. On the contrary, a diminished yield was achieved using 10 equiv. of norbornene (entry 12, 31%). Different photocatalysts, including strongly oxidizing ones such as **PC5** and **PC6** (entries 13-14) were unable to induce the formation of **4a**. The product formed in traces only operating at 25 °C and the *Z*- isomer of the substrate became the major product in this case. Finally, no traces of **4a** were observed in the absence of light (entry 15) or the Iridium photocatalyst.

With best condition in hand, we proceeded testing the generality of method. Model substrate **3a** in presence of norbornene afforded the corresponding product **4a** in 51% yield. Focusing our attention on the enynes, we observed that styrene decorated with EWGs, which usually make oxidation process more difficult, in this case worked well delivering products in moderate to good yield (**4b-g** 30-52%). Contrary to expectations, ortho-methyl substituted styrene **3h** provided us the corresponding product **4h** in 21% yield. Using racemic mixture of allylic substituted enynes the outcome was largely influenced by steric hindrance of the functionalization. Methyl substituted enynes delivered the corresponding product in 48% yield as a 2:1 mixture of diastereomers in which the most abundant showed methyl group in *anti* respect to fused cyclopropane ring. The presence of bulky phenyl group led to the formation of only the less hindered product **4j** in 39% yield. The use of trisubstituted styrene enabled us to access a [3.1.0] unit with 2 contiguous tetrasubstituted headbridging carbons in 42% yield. Finally, substituted norbornene, too, could be employed, as witnessed by **4l** that bears an unprotected carboxylic group (Scheme 13).



Scheme 13 scope of tetracyclic products with norbornene.

Regarding the limitations of the method, bromine in *para* position of the styryl fragment failed to afford product **4** as well as a nosyl fragment instead of the tosyl one. Probably as a result of steric hindrance near to alkene in the intermolecular step, propargylic substitutions were not tolerated. The presence of rigid tether like tosylamide was necessary as evidenced by its replacement with more flexible oxygen atom or methylene group that failed to afford product **4**. This could be ascribed to a pronounced Thorpe-Ingold effect at work in the cyclization[38]. Similarly, the use of 1,7-enynes or that of reagents with disubstituted alkynes did not allow the formation of the desired polycycle. Switching the attention on the alkene partner, we replaced norbornene with various terminal alkenes. Highly apolar ones gave however the corresponding product in low yield, most likely because of their poor miscibility with DMF (**4m**, 24%). A better outcome was obtained using vinylidenecyclohexane and the corresponding spirocyclic product was recovered in 40% yield. Several allylic substituted olefins can be employed (**4o-u**). In some of these cases the corresponding products were recovered in a mixture of diastereomers. Based on XRD structure of the most abundant diastereomer recovered from the reaction between **3a** and allyl alcohol (Figure 7). Remarkably, a variety of functional groups are tolerated by the method, affording the corresponding products in synthetically useful yields. The list includes esters, different alcohols, monosubstituted tosylamides, nitriles and silyl groups (Scheme 14).

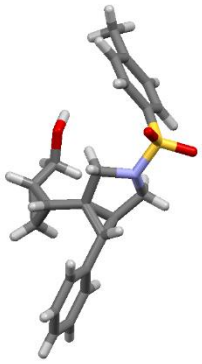
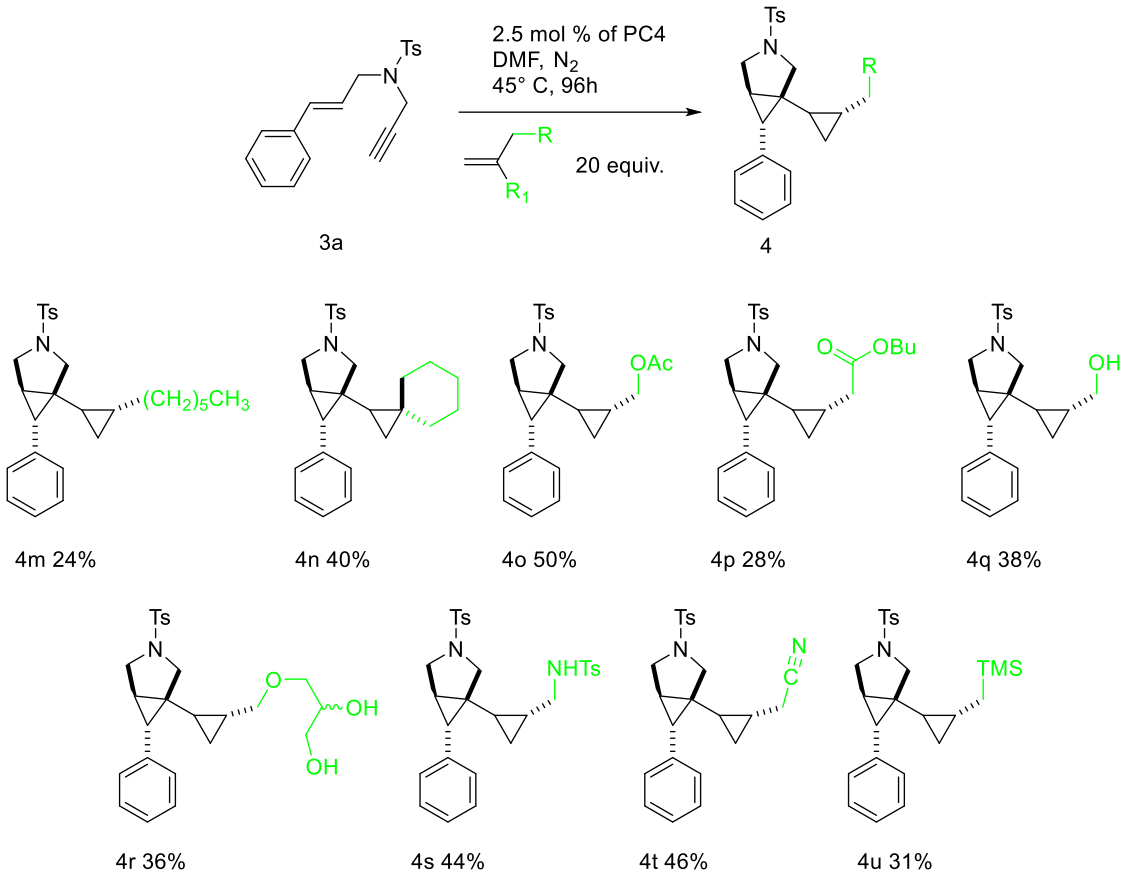


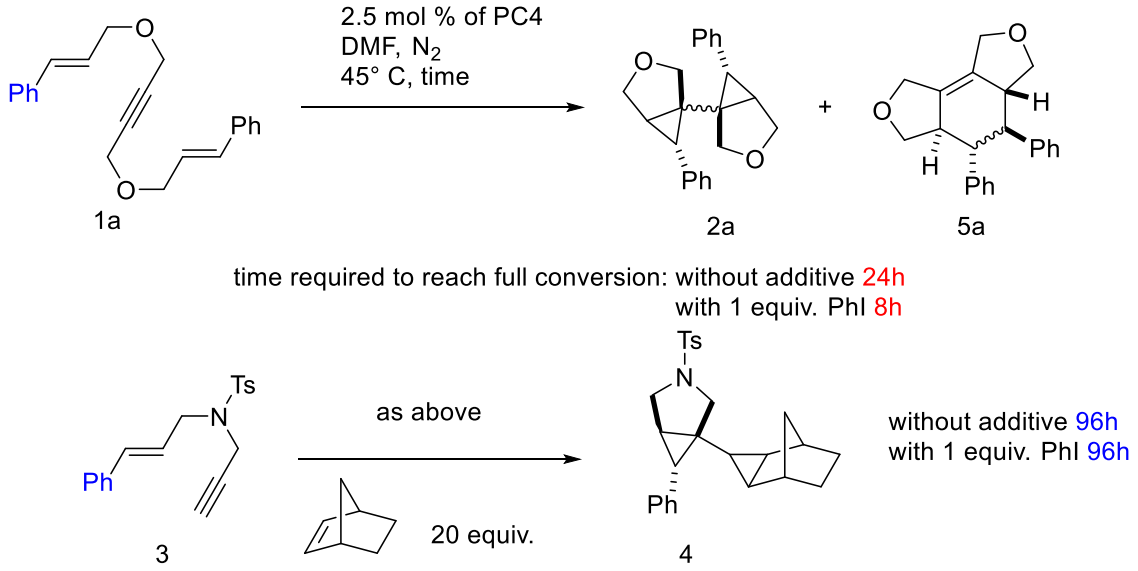
Figure 7 ORTEP of product 4q.



Scheme 14 scope of tricyclic product with terminal olefins.

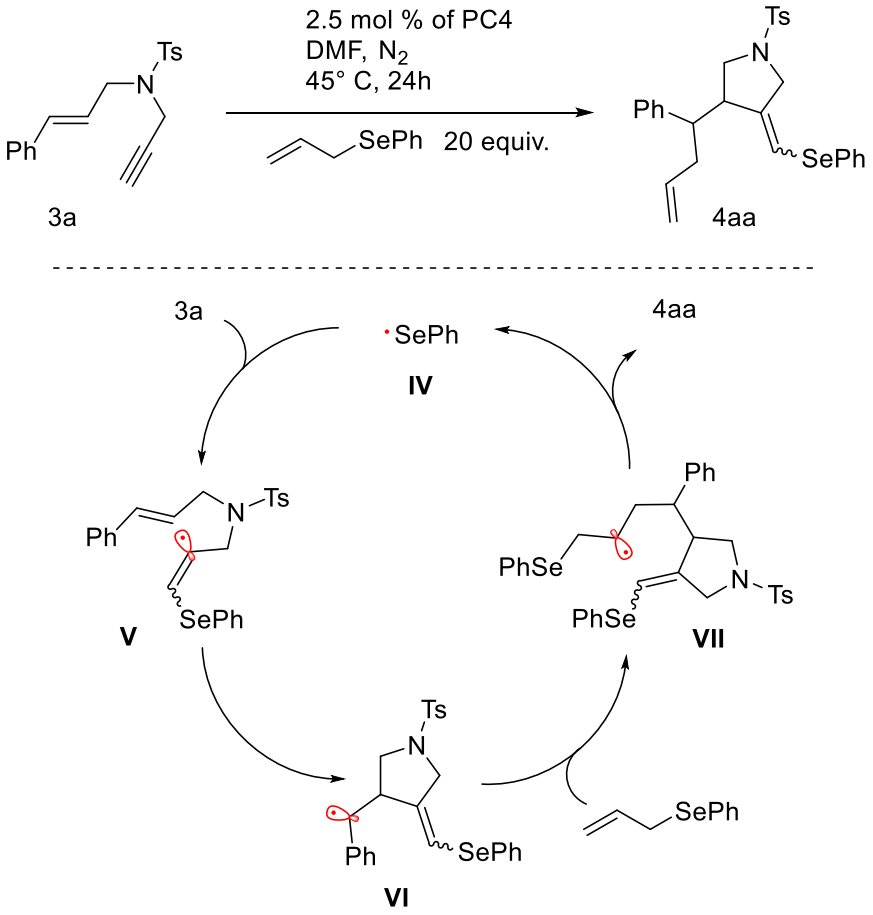
Regarding limitation of the method, trisubstituted olefins led to total loss of regio and stereochemical control. Alkenes that could readily undergo radical or ionic polymerization at high concentrations, such as acrylates and terminal styrenes, are similarly ineffective. The use of terminal allene failed to afford the corresponding vinylidene cyclopropane ring.

We next examined if the smart reinitiation tool that boosted the intramolecular cascade of dienynes **1** could have shortened the required reaction time also for the intermolecular process between **3** and alkenes. The intramolecular cascade descripted afforded tetracyclic and tricyclic structures whose combined yield was 91% yield with irradiation maintained for 24 h to complete the conversion of dienyne. The addition of 1 equiv. of iodobenzene led to the same result in a third of the time. Surprisingly, iodobenzene does not affect the reaction time for the intermolecular reaction with norbornene (Scheme 15).



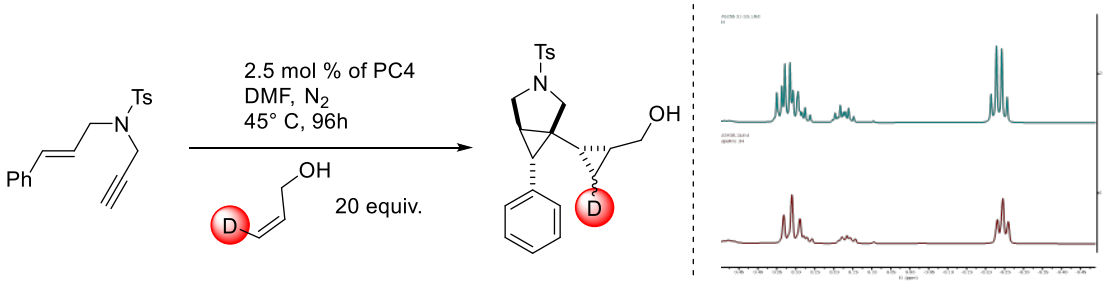
Scheme 15 striking kinetic differences.

We than tested phenyl allyl selenide as olefin partner. In contrast to the expectation, starting material disappear after 24 h but no traces of expected tricycle were found. However, product **4aa** was obtained as a mixture of E and Z isomers in excellent yield (81%). Based on literature study[39,40], we attempt to rationalise this observation. The formation of this derivative could be ascribed to a free-radical chain involving phenylselenyl radical **IV** (probably generated by β-homolytic fragmentation of allyl selenide). This Se- centered radical could add on the least hindered terminus of the alkyne unit, forming vinyl radical **V**. This highly reactive species would smoothly add on the styryl arm via *5-exo-trig* cyclization to afford benzyl radical **VI**. The latter might then intermolecularly add onto an additional molecule of allylphenylselenide to generate radical **VII**. This step is likely favoured by the molar excess of the alkene. Intermediate **VII** is prone toward β-fragmentation, which affords the desired product **4aa** and regenerates the phenylselenyl radical **IV** that further propagates the chain (Scheme 16).



Scheme 16 reaction of 3a with allylphenylselenide and possible reaction mechanism.

We then prepared a monodeuterated allyl alcohol in which the labelled isotope was selectively in a *Z*- arrangement with the methylene group to observe its relative position in polycycle **4**. the reaction of **3a** with deuterated compound afforded the corresponding monodeuterated **4q** in 37% yield, in accordance with the precedent observation. Deuterium atom was evenly spread on the methylene in the tethered cyclopropane ring as shown by the absence of ^{2}J coupling in the NMR spectrum (Scheme 17).



Scheme 17 deuterium labelling experiment and H NMR of methylene in 4q compared to methylene in $d_1$4q.

In order to rationalize these experimental evidences, we performed DFT modelling studies to understand the differences between the intramolecular reaction of dienyenes and present intermolecular sequences. Calculations were performed at the M06/Def2-TZVP level, which already proved reliable to assess related photochemical processes, using DMF as implicit solvent.

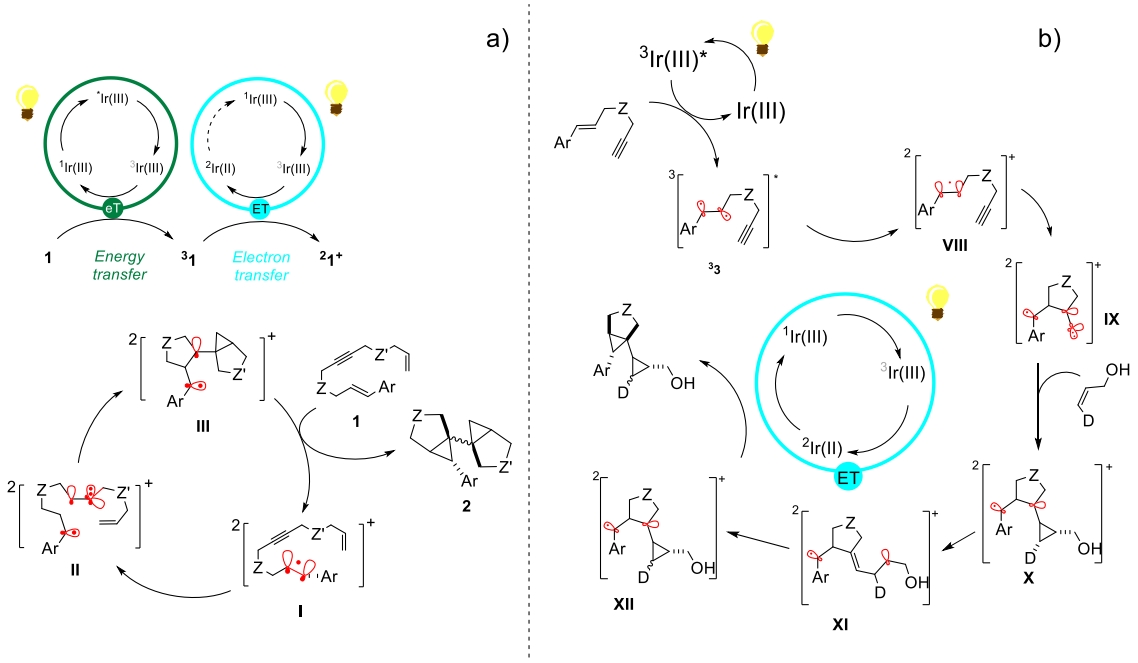
Enyne with an oxygen atom instead of tosylamide and allylic alcohol were selected to minimize computational cost. According to DFT calculation, any electron transfer process between ^{3}Ir(III) and substrates were thermodynamically disfavored with calculated ΔG of approximately +17.0 Kcal/mol for both oxidation and reduction process. On the contrary, the triplet state energies of the catalyst and the enyne are comparably (+48.3 and +48.8 kcal/mol respectively) and an energy transfer process can easily take place. Moreover, both these scenarios are backed by ample literature precedents on related substrates[28]. However, even after energy transfer occurred, we are unable to determine any energetically possible pathway that afforded product **4**. ^{3}**3** could undergoes 5-*exo-trig* cyclization to provide monocyclic triplet with a benzylic and a vinylic radical arm. Unfortunately, the latter is unable to participate in an intermolecular cyclopropanation. The addition of unstable vinyl radical to an alkene moiety would be possible only if driven by polarity reversal, therefore in presence of strongly polarized groups.

In an alternative scenario, the oxidation of ^{3}**3** by means of a second photoexcited Iridium species is favourable according to DFT (calculated ΔG = -30.8 kcal/mol). This would led to the formation of radical cation **VIII**. This intermediate can undergo *5-exo-dig* cyclization through a low barrier (**TS(VIII-IX)**, +8.7 kcal/mol in ΔG), forming **IX**, which is slightly less stable than **VIII** (by +4.0 kcal/mol in ΔG). The latter has a carbenoid character that allows its concerted cycloaddition with an alkene that delivers intermediate **X**. The process appears to be barrierless, in analogy to observations made on the intramolecular cascade of dienynes. We model the ΔG of a putative propagation step that involves a molecule of **3** and **X** to afford one of product **4** together with **VIII**. However, in stark contrast to the intramolecular case, a similar step has no longer a negative ΔG. The calculated value of +2.4 kcal/mol suggests its reduced likeliness. The overall lower steric congestion of intermediate **X**, compared with that of **III** (Scheme 18a), likely give to the former a sufficiently higher relative stability to hinder its oxidation of an additional substrate molecule.

A reductive process was required from intermediate **X** to afford final product **4**. Despite a strongly negative ΔG (-67.8 Kcal/mol) that distinguished the reductive quenching of **X** by ^{2}Ir(II), the latter was present in very low concentration. Even if concentration cannot be modelized, the difficulty to circumvent this statistic hurdle should be obvious.

Intermediate **X** undergoes ring opening reaction of cyclopropane ring forming intermediate **XI** through a barrier of +10.5 Kcal/mol that can reform cyclopropane ring

through the same barrier affording intermediate XII. This series of ring opening/closing reaction led to establish a formal equilibrium between **X** and **XII** that persists until reduction event occurred delivering product **2**. The presence of deuterium labelling on both position of methylene in tethered cyclopropane can be explained with this succession of unselective cyclizations (Scheme 18b).



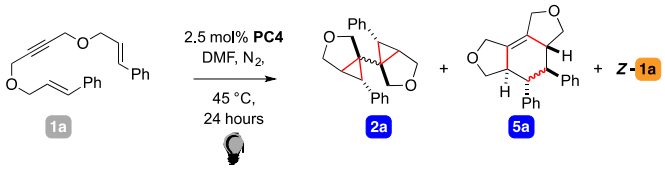
Scheme 18 proposed mechanistic scenario for intramolecular and intermolecular pathways.

Whit this background, we performed a series of experiments capable of evaluating the sensitivity of the method toward number of incident photons and photocatalyst concentration. In our opinion, any variation of these parameters should affect a process that involves two photon absorptions more than a Z/E isomerization, in which one photon is necessary to trigger energy transfer process (Figure 8, a)). We set up our home-made photoreactor to operate in the dark, except for the LED strip. We tuned its emission among different irradiation powers and measured (approximately) the corresponding Lux using a freeware smartphone app (Arduino science journal), achieving a robust level of reproducibility in the measured trends. The yield of all products was obtained from ^{1}H NMR analysis using TMB as internal standard.

Variations on the model reaction of **1a** were carried out at first (Figure 8, b)). A reaction carried out with an irradiation of ca. 550 Lux led to a moderate conversion upon 24 hours (entry 1). The cyclic products were retrieved in a combined 8% yield, and Z-**1a** was the main product in solution (17%). The same experiment performed by prolonging the irradiation for 72 hours (entry 2) showed a higher conversion and a comparable amount of cyclic products and isomerized substrate (31% and 35%, respectively). A similar conversion was achieved for the reaction irradiated 24 hours at ca. 2200 Lux (entry 3), although the cyclized products formed in a slightly higher amount than the isomerized one in this case (39% and 35%, respectively). Finally, pushing the emission of the LED strip at its most (ca. 6000 Lux, entry 4), the substrate was fully consumed over 24 hours. Moreover, cyclized products were observed in an excellent combined yield (91%) and the substrate isomerization became negligible. We thus took the conditions of entry **3**, in which conversion was not complete and the cyclization/isomerization similar, to test the effect of the catalyst concentration (Figure 8, c)). The reduction of the loading to 1 mol% reduced the conversion of **1a** (38%). The Z-**1a** product become the most abundant species formed (34%) and the combined yield of **2a** and **5a** was 29%. A strikingly different outcome was observed

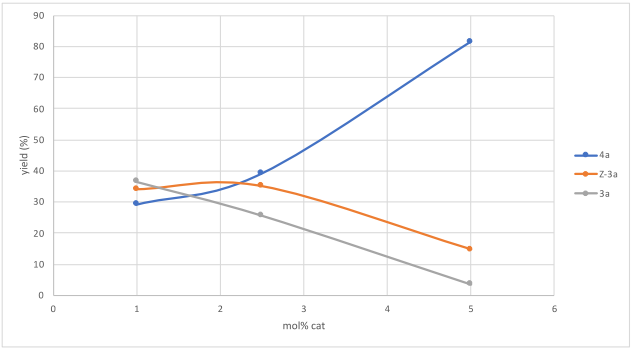
a)

b)

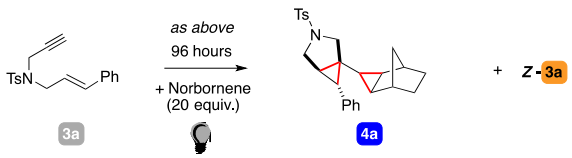


entry	Lux (appr.)	1a	2a + 5a	Z-1a
1	550	75%	8%	17%
2 (72 hours)	550	25%	31%	35%
3	2200	26%	39%	35%
4	6000	<1%	91%	<1%

c)



d)



entry	Lux (appr.)	3a	4a	Z-3a
1	1650	34%	27%	30%
2	2200	23%	32%	29%
3	4600	3%	36%	4%
4	6000	<1%	51%	<1%

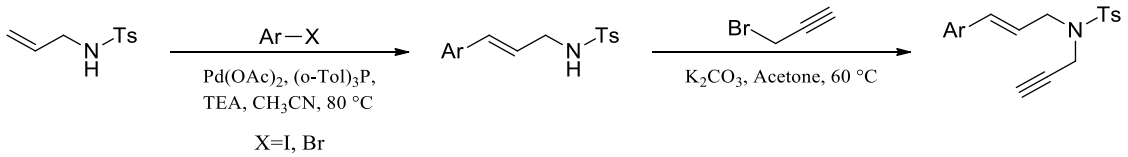
Figure 8 effects of the intensity of light and catalyst loading.

performing the reaction with 5 mol% of photocatalyst. The substrate was almost completely consumed (5%), **Z-1a** was retrieved in 15% yield and the cyclized species were the most abundant ones (81%). A similar trend was then observed for the intramolecular sequence (Figure 8, d)). At lower irradiation levels (entries 1-2), the substrate **3a** is not fully consumed upon 96 hours, and the ratio between the desired product **4a** and **Z-3a** is similar. On the contrary, the undesired isomerization is essentially silenced operating with higher irradiation intensities (entries 3-4), thus paralleling the outcome observed with **1a**.

Taken together, these results show that the isomerization of substrates is linearly influenced by both the intensity of light source and the catalyst concentration. At the same time, the net effect on the efficiency of the polycyclizations is much greater, further supporting the involvement of multi-photon events in the mechanisms of present cascades.

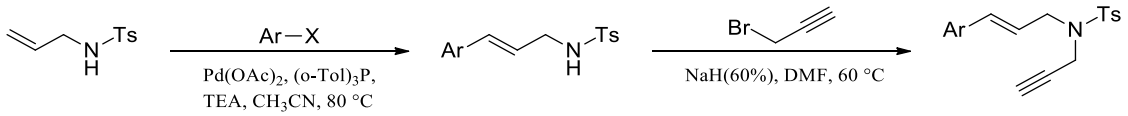
2.3 Experimental section

General procedure for the synthesis of enynes GP-1a



N-allyl-4-methylbenzenesulfonamide (1 equiv.), $(o\text{-Tol})_3P$ (0.1 equiv.) and $Pd(OAc)_2$ (0.05 equiv.) were sequentially added to a Schlenk tube equipped with magnetic stirring bar. CH_3CN (0.41 M), TEA (2 equiv.) and the desired aryl halide (1 equiv.) were added under N_2 atmosphere and the mixture was stirred at 80 °C for 3 hours. A second batch of the desired aryl halide (0.42 equiv.), $Pd(OAc)_2$ (0.026 equiv.) and $(o\text{-Tol})_3P$ (0.05 equiv.) were then added. The mixture was stirred at 80 °C for further 6 hours, allowed to cool to room temperature, diluted with water and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentred under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 9:1). The substituted cinnamyl tosylamide (1 equiv.) was dissolved in acetone (0.2 M). K_2CO_3 (3 equiv.) and propargyl bromide (85% in toluene, 1.5 equiv.) were then added. The mixture was subsequently placed in a preheated oil bath at 60 °C and stirred overnight. After consumption of the starting material, the reaction mixture was cooled down to room temperature and water was added. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 8:2).

General procedure for the synthesis of enynes GP-1b



The Heck-type coupling was performed according to the above-mentioned procedure. Then, the resulting tosylamide (1 equiv.) was dissolved in DMF (0.2 M). NaH (60% in mineral oil, 1.3 equiv.) was added slowly at 0° C under vigorous stirring. The resulting mixture was stirred for 1 hour at room temperature prior to the addition of a propargyl bromide solution (85% in toluene, 1.5 equiv.). The resulting mixture was then heated at

60° C for 2 hours. After completion, the reaction mixture was cooled down to room temperature and water was added. The mixture was extracted with EtOAc (3 x 30 mL) and the organic layers washed with a sat. LiCl solution. The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (nhexane/EtOAc 8:2).

General procedure for the synthesis of enynes GP-1c

Cinnamaldehyde (1.89 mL, 15 mmol) and 4-methylbenzenesulfonamide (2.56 g, 15 mmol) were dissolved in dry toluene (90 mL) and a catalytic amount of a solution of BF_3Et_2O (0.8 M, 75μL) was added under stirring. The resulting mixture was refluxed using a Dean-Stark apparatus. After 2 hours the solution was cooled to room temperature and EtOAc (45 mL) was added. The mixture was then washed with a solution of NaOH 1 N, water and saturated solution of NH_4Cl in this order. The organic layer was dried with Na_2SO_4 and the solvent was evaporated affording **4-methyl-N-((1E,2E)-3-phenylallylidene)benzenesulfonamide** that was used without further purification. To a solution of **4-methyl-N-((1E,2E)-3-phenylallylidene)benzenesulfonamide** (1 equiv.) in THF (0.17 M) under N_2 atmosphere at -30 °C, a solution of desired Grignard reagent (1.1 equiv.) was added under vigorous magnetic stirring and the solution was allowed to warm to room temperature. After 3 hours the mixture was quenched with saturated solution of NH_4Cl and extracted with EtOAc (3X). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated under vacuum. The resulting crude was purified by chromatography on silica gel (nhexane/EtOAc 7:3). The substituted cinnamyl tosylamide (1 equiv.) was dissolved in acetone (0.2 M). K_2CO_3 (3 equiv.) and propargyl bromide (85% in toluene, 1.5 equiv.) were then added. The mixture was subsequently placed in a preheated oil bath at 60 °C and stirred overnight. After consumption of the starting material, the reaction mixture was cooled down to room temperature and water was added. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 8:2).

General procedure for the synthesis of enynes GP-1d

To a solution of 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (1 equiv.), (E)-2-methyl-3-phenylprop-2-en-1-ol (1 equiv) and triphenyl phosphine (1equiv.) in dry THF (0.13 M), DIAD (1equiv.) was added at 0° C. The mixture was allowed to warm to room temperature and stirred 24 hours. After completation monitoring by TLC, the solvent was evaporated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 8:2).

General procedure GP-2

To a vial charged with substrate (1eq.) and PC4 (0.025 equiv), dry and degassed DMF (0.4 M) were added. The solution was transferred in a 5 mm NMR tube and degassed with three freezing-pump cycles. The homogeneous solution was placed in an oil bath at 45° C and irradiated with LED stripes until completion monitoring by TLC, tipically for 96 hours. The mixture was then concentrated and the residue was purified by chromatography on silica gel.

Following the literature procedure ***N*-cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 3a** was isolated as a white solid. (1.9 g, 90%). The spectral data for this compound corresponds to the literature[41]. **^{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).

yl)benzenesulfonamid Following the **GP-1a** product **(*E*)-*N*-(3-(4-chlorophenyl)allyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 3b** was isolate as white solid. (254 mg, 80%) The spectral data for this compound corresponds to the literature. [42] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 – 7.23 (m, 6H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.05 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.11 (d, *J* = 2.4 Hz, 2H), 3.98 – 3.96 (m, 2H), 2.42 (s, 3H), 2.04 (s, 1H).

Following the **GP-1a** product **(E)-4-methyl-N-(prop-2-yn-1-yl)-N-(3-(4(trifluoromethyl)phenyl)allyl)benzenesulfonamide 3c** was isolate as white solid. (195 mg, 29%). The spectral data for this compound corresponds to the literature. [43] **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.30 (m, 4H), 6.62 (d, *J* = 16.1 Hz, 2H), 6.18 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.16 (d, *J* = 2.5 Hz, 2H), 4.04 (dd, *J* = 6.7, 1.4 Hz, 2H), 2.46 (s, 3H), 2.09 (t, *J* = 2.5 Hz, 1H).

Following the **GP-1a** product **(*E*)-4-methyl-*N*-(prop-2-yn-1-yl)-*N*-(3-(3(trifluoromethyl)phenyl)allyl)benzenesulfonamide 3d** was isolate as colourless oil. (216 mg, 25%) The spectral data for this compound corresponds to the literature[44]. **^{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).

Following the **GP-1a** product **(*E*)-*N*-(3-(3-fluorophenyl)allyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 3e** was isolate as white solid. (328 mg, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* = 7.76 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H) 7.27 (m, 1H), 7.09 (d, *J* = 7.7 Hz, 2H), 7.01 (m, 1H), 6.95 (tdd, *J* = 8.4, 2.5, 0.8, 1H), 6.54 (d, *J* = 15.9 Hz,

1H), 6.08 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.13 (d, *J* = 2.5, 2H), 3.99 (dd, *J* = 6.8, 1.1, 2H), 6.44 (s, 3H), 2.06 (t, *J* = 2.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.8, 138.6, 138.5, 136.3, 136.1, 133.7, 130.2 (d, *J* = 8.5 Hz), 128.8 (d, *J* = 179.2 Hz), 124.6, 122.5, 115.0 (d, *J* = 21.4 Hz), 113.1 (d, *J* = 21.9 Hz), 74.0, 48.5, 36.2, 21.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.28.

Following the **GP-1b** product **(E)-N-(3-(3-cyanophenyl)allyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide 3f** was isolate as brown solid. (667.0 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.51 (m, 1H), 7.44 (t, *J* = 8.0 Hz, 0H), 7.34 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 15.9 Hz, 0H), 6.18 (dt, *J* = 15.8, 6.6 Hz, 0H), 4.15 (d, *J* = 2.3 Hz, 1H), 4.03 (d, *J* = 6.6 Hz, 1H), 2.46 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.9, 137.4, 136.0, 132.2, 131.3, 130.6, 130.1, 129.6, 129.5, 127.8, 126.2, 118.6, 112.9, 76.5, 74.1, 48.4, 36.3, 21.6. **(ESI)-MS** calcd for $C_{20}H_{18}N_2NaO_2S$ $[M+Na]^+$ 373.42 found 373.32

Following the **GP-1b** product **(E)-N-(3-(2-cyanophenyl)allyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide 3g** was isolate as yellow oil. (229 mg, 44%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.65 – 7.51 (m, 3H), 7.38 – 7.30 (m, 3H), 7.02 – 6.85 (m, 1H), 6.33 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.14 (d, *J* = 2.5 Hz, 2H), 4.05 (dd, *J* = 6.8, 1.4 Hz, 2H), 2.44 (d, *J* = 0.7 Hz, 3H), 2.09 (t, *J* = 2.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.9 (Cq), 139.3 (Cq), 135.6 (Cq), 133.0 (CH), 132.9 (CH), 130.4 (CH), 129.7 (CH), 128.9 (CH), 128.2 (CH), 127.8 (CH), 125.9 (CH), 117.6 (Cq), 111.2 (Cq), 76.2 (Cq), 74.4 (CH), 48.7 (CH_2), 36.5 (CH_2), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{18}N_2NaO_2S$ $[M+Na]^+$ 373.42 found 373.13

Following the **GP-1a** product **(*E*)-4-methyl-*N*-(prop-2-yn-1-yl)-*N*-(3-(*o*-tolyl)allyl)benzenesulfonamide 3h** was isolate as white solid. (500 mg, 61%) The spectral data for this compound corresponds to the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.35 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.18 – 7.12 (m, 3H), 6.81 (d, *J* = 15.6 Hz, 1H), 5.95 (dt, *J* = 15.4, 6.9 Hz, 1H), 4.14 (d, *J* = 2.5 Hz, 2H), 4.01 (d, *J* = 6.9 Hz, 2H), 2.44 (s, 3H), 2.31 (s, 3H), 2.05 (s, 1H).

Following the **GP-1c** product **(E)-4-methyl-N-(4-phenylbut-3-en-2-yl)-N-(prop-2-yn-1-yl)benzenesulfonamide 3i** was isolate as white solid. (245.0 mg, 54%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 1H), 7.37 – 7.21 (m, 7H), 6.41 (dd, *J* = 16.1, 1.5 Hz, 1H), 6.13 (dd, *J* = 16.1, 5.5 Hz, 1H), 4.80 – 4.68 (m, 1H), 4.19 (dd, *J* = 18.5, 2.5 Hz, 1H), 4.04 (dd, *J* = 18.5, 2.5 Hz, 1H), 2.44 (s, 3H), 1.41 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.4, 137.8, 136.3, 131.9, 129.5, 128.7, 128.6, 127.9, 127.6, 126.5, 80.3, 72.5, 54.8, 32.5, 21.5, 17.9. **ESI-MS** calcd for $C_{20}H_{21}NNaO_2S$ $[M+Na]^+$ 362.12, found: 361.98.

Following the **GP-1c** product **(E)-N-(1,3-diphenylallyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide 3j** was isolate as white solid. (245.0 mg, 54%)**. ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.48 – 7.05 (m, 13H), 6.53 (dd, *J* = 15.9, 8.4 Hz, 1H), 6.31 (d, *J* = 15.9 Hz, 1H), 5.73 (d, *J* = 8.4 Hz, 1H), 4.27 (dd, *J* = 18.6, 2.4 Hz, 1H), 3.83 (dd, *J* = 18.6, 2.5 Hz, 1H), 2.33 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.4, 138.2, 137.4, 136.3, 134.1, 129.2, 128.7, 128.5, 128.1, 128.1, 128.0, 127.9, 126.5, 125.2, 79.8, 72.9, 63.4, 33.9, 21.5. **ESI-MS** calcd for $C_{25}H_{23}NNaO_2S$ $[M+Na]^+$ 424.13, found: 423.95.

Following the **GP-1d** product **(E)-4-methyl-N-(2-methyl-3-phenylallyl)-N-(prop-2-yn-1-yl)benzenesulfonamide 3k** was isolate as white solid. (569.2 mg, 57%)**. ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 1H), 7.53 – 7.16 (m, 8H), 6.50 (s, 1H), 4.12 (d, *J* = 2.4 Hz, 2H), 3.91 (s, 2H), 2.46 (s, 3H), 1.95 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.6, 137.0, 136.0, 131.9, 130.0, 129.5, 128.9, 128.2, 127.9, 126.9, 76.4, 73.9, 55.0, 35.5, 21.6, 15.7. **ESI-MS** calcd for $C_{25}H_{23}NNaO_2S$ $[M+Na]^+$ 424.13, found: 423.95. **ESI-MS** calcd for $C_{20}H_{21}NNaO_2S$ $[M+Na]^+$ 362.12, found: 361.97.

Following the literature procedure[45] **(Z)-prop-2-en-3-d-1-ol** was isolated as a clear liquid (302.0 mg, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.06 – 5.94 (m, 0.92H), 5.31 – 5.23 (m, 0.11H), 5.14 (d, *J* = 10.4 Hz, 0.69H), 4.16 (d, *J* = 4.7 Hz, 2H). The analytical data for this compound correspond to the literature.

(1S,5R,6S)-6-phenyl-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.02,4]octan-3-yl)-3-azabicyclo[3.1.0]hexane. 4a was isolated following the **GP-2** using **3a** (65.0 mg, 0.2 mmol) and norbornene (376.6 mg, 4 mmol) as reagents. Yield **51**% (33.2 mg, 0.102 mmol). **^{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 (CH2), 50.4 (CH2), 35.7 (CH), 35.4 (CH), 34.0 (Cq), 29.9 (CH), 29.3 (CH2), 29.2 (CH2), 28.1 (CH2), 25.7 (CH), 23.4 (CH), 21.6 (CH), 21.5 (CH), 11.3 (CH). **ESI-HRMS** cald for $C_{26}H_{30}NO_2S$ $[M+H]^+$ 420.1992, found 420.1991.

(1S,5R,6S)-6-(4-chlorophenyl)-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.0^{2,4}]octan-3-yl)-3-azabicyclo[3.1.0]hexane 4b was isolated following the **GP-X** using **3b** (73.8 mg, 0.2 mmol) and norbornene (376.6 mg, 4 mmol) as reagents. Yield **48**% (44.0 mg, 0.096 mmol). Pale-yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 3.61 (d, *J* = 9.3 Hz, 1H), 3.57 (d, *J* = 9.3 Hz, 1H), 3.10 (dd, *J* = 9.2, 3.8 Hz, 1H), 3.00 (d, *J* = 9.3 Hz, 1H), 2.44 (s, 3H), 2.14 – 2.07 (m, 1H), 2.03 (d, *J* = 4.1 Hz, 1H), 1.81 – 1.75 (m, 1H), 1.54 (t, *J* = 3.9 Hz, 1H), 1.38 – 1.18 (m, 2H), 1.14 – 0.95 (m, 2H), 0.64 (d, *J* = 10.6 Hz, 1H), 0.52 (t, *J* = 2.8 Hz, 1H), 0.45 (d, *J* = 10.6 Hz, 1H), 0.35 (dd, *J* = 7.2, 2.8 Hz, 1H), 0.17 (dd, *J* = 7.2, 2.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5 (Cq), 136.1 (Cq), 133.8 (Cq), 131.7 (Cq), 130.3 (2CH), 129.7 (2CH), 128.0 (2CH), 127.5 (CH), 54.0 (CH_2), 50.4 (CH_2), 35.7 (CH), 35.5 (CH), 34.1 (Cq), 29.33 (CH_2), 29.25 (CH_2), 29.2 (CH), 28.2 (CH_2), 25.9 (CH), 23.4 (CH), 21.7 (CH), 21.6 (CH_3), 11.2 (CH). **ESI-MS** calcd for $C_{26}H_{28}ClNNaO_2S$ $[M+Na]^+$ 476.14, found: 476.47.

(1S,5R,6S)-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.0^{2,4}]octan-3-yl)-6-(4-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexane 4c was isolated following the **GP-2** using **3c** (76.0 mg, 0.2 mmol) and **norbornene** (376.6 mg, 4 mmol) as reagents. Yield

37% (29.1 mg, 0.074 mmol). White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 3.63 (dd, *J* = 13.9, 9.4 Hz, 2H), 3.11 (dd, *J* = 9.3, 3.8 Hz, 1H), 3.01 (d, *J* = 9.4 Hz, 1H), 2.45 (s, 3H), 2.15 – 2.06 (m, 2H), 1.74 (s, 1H), 1.63 (t, *J* = 3.9 Hz, 1H), 1.27 (dd, *J* = 10.0, 3.2 Hz, 2H), 1.14 – 0.96 (m, 2H), 0.62 (d, *J* = 10.6 Hz, 1H), 0.53 (s, 1H), 0.45 (d, *J* = 10.6 Hz, 1H), 0.36 (dd, *J* = 7.5, 2.7 Hz, 1H), 0.18 (d, *J* = 7.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.6 (Cq), 141.9 (q, *J* = 1.3 Hz, Cq), 133.7 (Cq), 129.7 (2CH), 129.2 (2CH), 128.2 (q, *J* = 32.2 Hz. Cq), 127.5 (2CH), 124.8 (q, *J* = 3.8 Hz, 2CH), 124.3 (q, *J* = 271.3 Hz, Cq), 54.0 (CH_2), 50.3 (CH_2), 35.7 (CH), 35.4 (CH), 34.6 (Cq), 29.6 (CH), 29.3 (CH_2), 29.2 (CH_2), 28.2 (CH_2), 26.1 (CH), 23.6 (CH), 21.8 (CH), 21.6(CH_3), 11.1 (CH). **^{19}F NMR (565 MHz, $CDCl_3$)** δ = -62.19. **ESI-MS** calcd for $C_{27}H_{28}F_3NNaO_2S$ $[M+Na]^+$ 510.17, found: 510.19.

(1S,5R,6S)-3-tosyl-1-((1R,2S,3R,4R,5S)-tricyclo[3.2.1.02,4]octan-3-yl)-6-(3-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexane 4d was isolated following the **GP-2** using **3d** (76.0 mg, 0.19 mmol) and **norbornene** (359.5 mg, 3.8mmol) as reagents. Yield **49**% (47.4 mg, 0.093 mmol). White solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.22 (m, 6H), 3.64 (d, *J* = 9.4 Hz, 1H), 3.60 (d, *J* = 9.4 Hz, 1H), 3.13 (dd, *J* = 9.4, 3.8 Hz, 1H), 3.04 (d, *J* = 9.4 Hz, 1H), 2.45 (s, 3H), 2.14 – 2.01 (m, 2H), 1.78 (brs, 1H), 1.61 (t, *J* = 3.9 Hz, 1H), 1.34 – 1.21 (m, 2H), 1.13 – 0.97 (m, 2H), 0.66 – 0.58 (m, 1H), 0.52 (t, *J* = 3.0 Hz, 1H), 0.45 (d, *J* = 10.7 Hz, 1H), 0.37 (d, *J* = 7.3 Hz, 1H), 0.19 (d, *J* = 7.4 Hz, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ = 143.6 (Cq), 138.7 (Cq), 133.8 (Cq), 132.50 (q, *J* = 1.3 Hz, CH), 130.24 (q, *J* = 32.0 Hz, Cq), 129.8 (2CH), 128.3 (CH), 127.5 (2CH), 125.47 (q, *J* = 3.8 Hz, CH), 124.23 (q, 122.75 *J* = 272.5 Hz, Cq),122.75 (q, *J* = 3.9 Hz, CH), 54.0 (CH_2), 50.4 (CH_2), 35.7 (CH), 35.4 (CH), 34.4 (Cq), 29.5 (CH), 29.3 (CH_2), 29.2 (CH_2), 28.1 (CH_2), 26.3 (CH), 23.7 (CH), 21.9 (CH), 21.6 (CH_3), 11.2 (CH). **^{19}F NMR (565 MHz, $CDCl_3$)** δ = -62.47. **ESI-MS** calcd for $C_{27}H_{28}F_3NNaO_2S$ $[M+Na]^+$ 510.17, found: 510.46.

(1S,5R,6S)-6-(3-fluorophenyl)-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.0^{2,4}]octan-3-yl)-3-azabicyclo[3.1.0]hexane 4e was isolated following the **GP-2** using **3e** (72.5 mg, 0.21 mmol) and **norbornene** (397.3 mg, 4.2 mmol) as reagents. Yield **52**% (48.6 mg, 0.109 mmol). White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 8.1 Hz, 2H), 7.35

(d, *J* = 8.1 Hz, 2H), 7.25 – 7.15 (m, 1H), 6.93 – 6.76 (m, 3H), 3.62 (d, *J* = 9.3 Hz, 1H), 3.58 (d, *J* = 9.4 Hz, 1H), 3.11 (dd, *J* = 9.3, 3.8 Hz, 1H), 3.01 (d, *J* = 9.3 Hz, 1H), 2.45 (s, 3H), 2.12 – 2.02 (m, 2H), 1.80 (brs, 1H), 1.57 (t, *J* = 4.0 Hz, 1H), 1.36 – 1.20 (m, 2H), 1.14 – 0.98 (m, 2H), 0.64 (d, *J* = 10.8 Hz, 1H), 0.54 (brs, 1H), 0.45 (d, *J* = 10.6 Hz, 1H), 0.36 (d, *J* = 7.2 Hz, 1H), 0.21 (d, *J* = 6.2 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ = 162.6 (d, *J* = 244.8 Hz, Cq), 143.6 (Cq), 140.2 (d, *J* = 7.7 Hz, Cq), 133.8 (Cq), 129.7 (2CH), 129.3 (d, *J* = 8.5 Hz, CH), 127.5 (2CH), 124.7 (d, J = 2.7 Hz, CH), 115.7 (d, *J* = 21.5 Hz, CH), 112.84 (d, *J* = 21.1 Hz, CH), 54.0 (CH_2), 50.4 (CH_2), 35.7 (CH), 35.5 (CH), 34.3 (Cq), 29.6 (d, *J* = 2.0 Hz, CH), 29.3 (CH_2), 29.2 (CH_2), 28.2 (CH_2), 26.1 (CH), 23.5 (CH), 21.8 (CH), 21.6 (CH_3), 11.2 (CH). **^{19}F NMR** (565 MHz, CDCl3) δ -114.04. **ESI-MS** calcd for $C_{26}H_{29}FNO_2S$ $[M+H]^+$ 438.19, found: 438.04.

3-((1S,5R,6S)-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.02,4]octan-3-yl)-3-azabicyclo[3.1.0]hexan-6-yl)benzonitrile 4f was isolated following the **GP-2** using **3f** (70.0 mg, 0.2 mmol) and **norbornene** (376.6 mg, 4.0 mmol) as reagents. Yield **30**% (26.8 mg, 0.060 mmol). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.70 (d, *J* = 8.3 Hz, 2H), 7.49 – 7.44 (m, 1H), 7.40 – 7.34 (m, 5H), 3.64 (d, *J* = 9.4 Hz, 1H), 3.60 (d, *J* = 9.5 Hz, 1H), 3.09 (dd, *J* = 9.3, 3.8 Hz, 1H), 3.00 (d, *J* = 9.4 Hz, 1H), 2.45 (s, 3H), 2.10 (d, *J* = 3.8 Hz, 2H), 1.79 – 1.74 (brs, 1H), 1.59 (t, *J* = 3.9 Hz, 1H), 1.37 – 1.20 (m, 2H), 1.14 – 0.97 (m, 2H), 0.62 (d, *J* = 10.7 Hz, 1H), 0.50 (t, *J* = 2.7 Hz, 1H), 0.46 (d, *J* = 10.7 Hz, 1H), 0.36 (dd, *J* = 7.2, 2.6 Hz, 1H), 0.21 – 0.11 (m, 1H). **^{13}C NMR (101 MHz, CDCl3)** δ = 143.7 (Cq), 139.4 (Cq), 133.7 (CH) ,133.6 (Cq), 132.3 (CH), 129.8 (2CH), 129.7 (CH), 128.8 (CH), 127.5 (2CH), 119.0 (Cq), 112.0 (Cq), 53.9 (CH_2), 50.2 (CH_2), 35.7, 35.4, 34.5 (Cq), 29.3 (CH_2), 29.20 (CH_2), 29.15 (CH_2), 28.2 (CH), 26.1 (CH), 23.7 (CH), 21.9 (CH), 21.6 (CH_2), 11.1 (CH). **ESI-MS** calcd for $C_{27}H_{28}N_2NaO_2S$ $[M+Na]^+$ 467.18, found: 467.12.

2-((1S,5R,6S)-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.02,4]octan-3-yl)-3-azabicyclo[3.1.0]hexan-6-yl)benzonitrile 4g was isolated following the **GP-2** using **3g** (72.0 mg, 0.2 mmol) and **norbornene** (376.6 mg, 4.0 mmol) as reagents. Yield **51**% (46.5 mg, 0.105 mmol). White solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.77 – 7.71 (m, 2H), 7.68 – 7.59 (m, 1H), 7.52 – 7.46 (m, 1H), 7.40 – 7.20 (m, 4H), 3.81 (d, *J* = 9.5 Hz, 1H), 3.68 (d, *J* = 9.5 Hz, 1H), 3.22 (dd, *J* = 9.5, 3.9 Hz, 1H), 3.16 (d, *J* = 9.5 Hz, 1H), 2.45 (s, 3H), 2.23 – 2.10 (m, 2H), 1.70 (t, *J* = 4.0 Hz, 1H), 1.60 – 1.54 (brs, 1H), 1.37 – 1.17 (m,

2H), 1.11 – 1.04 (m, 1H), 1.00 – 0.90 (m, 1H), 0.76 (brs, 1H), 0.70 (d, *J* = 10.6 Hz, 1H), 0.45 (d, *J* = 10.6 Hz, 1H), 0.40 (d, *J* = 7.1 Hz, 1H), -0.07 (d, *J* = 5.6 Hz, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ = 143.6 (Cq), 142.1 (Cq), 134.0 (Cq), 132.7 (CH), 132.2 (CH), 129.8 (2CH), 129.7 (CH), 127.5 (2CH), 126.7 (CH), 118.3 (Cq), 114.4 (Cq), 54.2 (CH_2), 50.2 (CH_2), 35.6, 35.3, 35.0 (Cq), 29.22 (CH_2), 29.17 (CH_2), 28.4(CH_2), 28.2 (CH), 24.8 (CH), 23.0 (CH), 21.6 (CH_3), 11.0 (CH). **ESI-MS** calcd for $C_{27}H_{28}N_2NaO_2S$ $[M+Na]^+$ 467.18, found: 466.70.

(1S,5R,6S)-6-(o-tolyl)-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.02,4]octan-3-yl)-3-azabicyclo[3.1.0]hexane 4h was isolated following the **GP-2** using **3h** (66.5 mg, 0.2 mmol) and **norbornene** (376.6 mg, 4.0 mmol) as reagents. Yield **21**% (18.0 mg, 0.041 mmol). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.71 (d, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.10 (dd, *J* = 14.3, 7.0 Hz, 3H), 6.99 (d, *J* = 6.1 Hz, 1H), 3.62 (d, *J* = 9.4 Hz, 2H), 3.21 (dd, *J* = 9.3, 3.9 Hz, 1H), 3.09 (d, *J* = 9.4 Hz, 1H), 2.44 (s, 3H), 2.23 (s, 3H), 2.08 (brs, 1H), 1.86 (d, *J* = 3.9 Hz, 1H), 1.70 – 1.62 (m, 2H), 1.35 – 1.17 (m, 2H), 1.12 – 0.93 (m, 2H), 0.56 (d, *J* = 11.0 Hz, 1H), 0.46 – 0.37 (m, 2H), 0.33 (d, *J* = 6.5 Hz, 1H), 0.12 (d, *J* = 6.8 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 143.5 (Cq), 138.1 (Cq), 135.5 (Cq), 134.1 (Cq), 129.7 (2CH), 129.6 (CH), 128.1 (CH), 127.5 (2CH), 126.2 (CH), 125.3 (CH), 53.8 (CH_2), 50.6 (CH_2), 35.6 (CH), 35.4 (CH), 33.9 (Cq), 29.4 (CH_2), 29.3 (CH_2), 28.8 (CH), 28.2 (CH_2), 24.4 (CH), 22.6 (CH), 21.6 (CH_3), 21.0 (CH), 19.8 (CH), 10.8 (CH). **ESI-MS** calcd for $C_{27}H_{31}KNO_2S$ $[M+K]^+$ 472.17, found: 472.17.

(1S,4R,5R,6S)-4-methyl-6-phenyl-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.02,4]octan-3-yl)-3-azabicyclo[3.1.0]hexane--(1S,4S,5R,6S)-4-methyl-6-phenyl-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.02,4]octan-3-yl)-3-azabicyclo[3.1.0]hexane 4i were isolated as a mixture of diastereoisomers following the **GP-2** using **3i** (67.8 mg, 0.2 mmol) and **norbornene** (376.6 mg, 4.0 mmol) as reagents. Yield **48**% (41.9 mg, 0.096 mmol, ratio 1:0.62).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 2HA, 2HB), 7.36 (d, *J* = 8.1 Hz, 1HA), 7.32 (d, *J* = 8.1 Hz, 1HB), 7.28 – 7.12 (m, 5HA,6HB), 6.93 (d, *J* = 7.4 Hz, 1HA), 4.04 (q, *J* = 6.3 Hz, 1HB), 3.64 (d, *J* = 9.4 Hz, 1HA), 3.52 (d, *J* = 10.4 Hz, 1HB), 3.47 – 3.37 (m, 1HA, 1HB), 3.13 (d, *J* = 9.4 Hz, 1HA), 2.46 (s, 3HA), 2.42 (s, 3HB), 2.31 (d, *J* = 4.0 Hz, 1HA), 2.14 (s, 1HB), 2.07 (s, 1HA), 1.80 (s, 1HB), 1.73 (s, 1HA), 1.61 (t, *J* = 4.0 Hz, 1HA), 1.47 (d, *J* = 6.0 Hz, 3HA), 1.32

– 1.21 (m, 2HA, 7HB), 1.13 – 0.92 (m, 2HA, 2HB), 0.70 – 0.60 (m, 1HA, 1HB), 0.59 – 0.49 (m, 1HA, 2HB), 0.49 – 0.39 (m, 1HA, 1HB), 0.29 – 0.22 (m, 1HB), 0.18 (dd, *J* = 7.1, 2.1 Hz, 1HA), 0.13 – 0.04 (m, 1HA). **(Major) ^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.5 (Cq), 137.8 (Cq), 133.3 (Cq), 129.6 (2CH), 129.1 (2CH), 127.9 (2CH), 127.8 (2CH), 126.0 (CH), 57.6 (CH), 57.3 (CH_2), 35.7 (CH), 35.45 (CH), 33.7 (CH), 31.1 (Cq), 29.36 (CH_2), 29.27 (CH_2), 28.2 (CH), 28.19 (CH_2), 23.3 (CH), 21.64 (CH), 21.48 (CH_3), 18.9 (CH_3), 11.5 (CH). **(Minor) ^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.2 (Cq), 137.3 (Cq), 137.2 (Cq), 129.8 (2CH), 128.7 (2CH), 127.8 (2CH), 127.0 (2CH), 125.8 (CH), 58.9 (CH), 53.0 (CH_2), 35.8 (CH), 35.54 (CH), 34.6 (Cq), 32.9 (CH), 30.2 (CH), 29.41 (CH_2), 29.29 (CH_2), 28.3 (CH_2), 23.8 (CH), 22.0 (CH_3), 21.59 (CH_3), 21.52 (CH), 10.7 (CH). **ESI-MS** calcd for $C_{27}H_{31}NNaO_2S$ $[M+Na]^+$ 456.20, found: 456.21.

(1S,4S,5R,6S)-4,6-diphenyl-3-tosyl-1-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.02,4]octan-3-yl)-3-azabicyclo[3.1.0]hexane 4j was isolated the **GP-2** using **3j** (80.2 mg, 0.2 mmol) and **norbornene** (376.6 mg, 4.0 mmol) as reagents. Yield **39**% (39.0 mg, 0.078 mmol). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.45 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.13 (m, 10H), 7.04 – 7.00 (m, 2H), 5.02 (s, 1H), 3.77 (d, *J* = 10.1 Hz, 1H), 3.53 (d, *J* = 10.0 Hz, 1H), 2.38 (s, 3H), 2.11 (brs, 1H), 1.80 (brs, 1H), 1.71 (d, *J* = 4.2 Hz, 1H), 1.68 (d, *J* = 4.2 Hz, 1H), 1.38 – 1.18 (m, 2H), 1.16 – 0.95 (m, 2H), 0.63 (d, *J* = 10.3 Hz, 1H), 0.57 (t, *J* = 3.0 Hz, 1H), 0.52 (dd, *J* = 7.4, 3.0 Hz, 1H), 0.44 (d, *J* = 10.5 Hz, 1H), 0.28 (d, *J* = 7.3 Hz, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ = 143.0 (Cq), 141.9 (Cq), 137.1 (Cq), 136.7 (Cq), 129.4 (2CH), 128.8 (2CH), 128.6 (2CH), 127.9 (2CH), 127.5 (CH), 127.0 (2CH), 126.6 (CH), 126.0 (2CH), 66.6 (CH), 54.5, 35.8 (CH), 35.6 (CH), 35.4, 34.2 (CH), 31.4 (CH), 29.4 (CH_2), 29.2 (CH_2), 28.2 (CH_2), 23.3 (CH), 21.50 (CH_3), 21.47 (CH), 11.2 (CH). **ESI-MS** calcd for $C_{32}H_{33}NNaO_2S$ $[M+Na]^+$ 518.21, found: 517.99.

(1R,5S,6R)-1-methyl-6-phenyl-3-tosyl-5-((1R,2S,3r,4R,5S)-tricyclo[3.2.1.02,4]octan-3-yl)-3-azabicyclo[3.1.0]hexane 4k was isolated following the **GP-2** using **3k** (67.8 mg, 0.2 mmol) and **norbornene** (376.6 mg, 4.0 mmol) as reagents. Yield **44**% (38.3 mg, 0.088 mmol). White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.33 – 7.14 (m, 5H), 3.71 (d, *J* = 9.0 Hz, 1H), 3.41 (d, *J* = 9.0 Hz, 1H), 2.97 (d, *J* = 8.9 Hz, 1H), 2.83 (d, *J* = 9.0 Hz, 1H), 2.46 (s, 3H), 2.30 (s, 1H), 2.13 (d, *J* = 16.2 Hz, 2H), 1.41 (h, *J* = 11.9, 11.3 Hz, 2H), 1.32 –

1.16 (m, 2H), 1.06 (s, 3H), 0.87 (dt, *J* = 27.2, 7.2 Hz, 1H), 0.78 – 0.65 (m, 2H), 0.55 (d, *J* = 10.6 Hz, 1H), 0.31 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.4 (Cq), 136.2 (Cq), 134.0 (Cq), 130.9 ($2CH_2$), 129.7 ($2CH_2$), 128.0 ($2CH_2$), 127.5 ($2CH_2$), 126.1 (CH), 56.6 (CH_2), 51.9 (CH_2), 35.9 (CH), 35.7 (CH), 32.3 (Cq), 30.8 (CH), 30.4 (Cq), 29.6 (CH_2), 29.5 (CH_2), 28.0 (CH_2), 21.6 (CH), 20.8 (CH), 19.9 (CH), 12.0 (CH), 10.7 (CH). **ESI-MS** calcd for $C_{27}H_{31}NNaO_2S$ $[M+Na]^+$ 518.20, found: 456.19.

(1R,2R,3S,4S,5R,6R)-3-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)tricyclo[3.2.1.02,4]octane-6-carboxylic acid--(1S,2S,3R,4R,5S,6S)-3-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)tricyclo[3.2.1.02,4]octane-6-carboxylic acid 4l was isolated as a mixture of isomers following the **GP-2** using **3a** (65 mg, 0.2 mmol) and 5-**norbornene-2-carboxylic acid** (predominantly endo) (560.7 mg, 4.0 mmol) as reagents. Yield **42**% (36.6 mg, 0.084 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 4H), 7.36 (dd, *J* = 8.0, 4.6 Hz, 4H), 7.30 – 7.23 (m, 4H), 7.22 – 7.14 (m, 2H), 7.13 – 7.05 (m, 4H), 3.66 – 3.56 (m, 4H), 3.22 (dd, *J* = 9.3, 3.8 Hz, 1H), 3.15 (dd, *J* = 9.2, 3.9 Hz, 1H), 3.08 (d, *J* = 9.4 Hz, 1H), 3.02 (d, *J* = 9.2 Hz, 1H), 2.66 (ddt, *J* = 15.6, 10.0, 4.5 Hz, 2H), 2.53 (d, *J* = 2.9 Hz, 1H), 2.47 (s, 3H), 2.46 (s, 3H), 2.25 – 2.18 (m, 2H), 2.07 (d, *J* = 4.5 Hz, 1H), 2.01 (d, *J* = 4.0 Hz, 1H), 1.87 (s, 1H), 1.70 – 1.51 (m, 6H), 0.84 – 0.75 (m, 2H), 0.71 – 0.58 (m, 6H), 0.58 – 0.44 (m, 2H), 0.40 – 0.30 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 179.74 (Cq), 179.71 (Cq), 143.6 (Cq), 143.5 (Cq), 137.12 (Cq), 137.11 (Cq), 134.3 (Cq), 133.8 (Cq), 129.76 (2CH), 129.75 (2CH), 129.0 (2CH), 128.7 (2CH), 128.0 (2CH), 127.9 (2CH), 127.5 (2CH), 127.4 (2CH), 126.1 (CH), 126.0 (CH), 53.83 (CH_2), 53.80 (CH_2), 50.43 (CH_2), 50.41 (CH_2), 46.7 (CH), 46.5 (CH), 39.5 (CH), 39.3 (CH), 36.3 (CH), 36.1 (CH), 33.7 (Cq), 33.6 (Cq), 31.8 (CH_2), 31.7 (CH_2), 30.0 (CH), 29.8 (CH), 29.43 (CH_2), 29.41 (CH_2), 25.9 (CH), 25.4 (CH), 22.7 (CH), 21.59 (CH_3), 21.56 (CH_3), 21.2 (CH), 19.0 (CH), 17.2 (CH), 11.3 (CH), 11.1 (CH). **ESI-MS** calcd for $C_{27}H_{29}NNaO_4S$ $[M+Na]^+$ 486.17, found: 486.20.

(1S,5R,6S)-1-((1S,2R)-2-hexylcyclopropyl)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexane dr 4:1 4m was isolated following the **GP-2** using **1a** (65.5 mg, 0.2 mmol) and **1-octene** (628 μL, 4.0 mmol) as reagents. Yield **24**% (21.0 mg, 0.048 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.09 (m, 5H), 3.69 (d, *J* = 9.2 Hz, 1H), 3.65 (d, *J* = 9.2 Hz, 1H), 3.14 (dd, *J* = 9.1,

3.8 Hz, 1H), 3.05 (d, *J* = 9.1 Hz, 1H), 2.18 (d, *J* = 4.2 Hz, 1H), 1.65 (t, *J* = 4.0 Hz, 1H), 1.32 – 0.73 (m, 13H), 0.59 – 0.44 (m, 1H), 0.43 – 0.26 (m, 1H), 0.17 (td, *J* = 8.5, 5.1 Hz, 1H), -0.55 (q, *J* = 5.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.5 (Cq), 137.5 (Cq), 132.8 (Cq), 129.6 (2CH), 129.0 (2CH), 127.9 (2CH), 127.7 (2CH), 125.9 (CH), 55.3 (CH_2), 50.2 (CH_2), 34.1 (Cq), 31.8 (CH_2), 29.9 (CH_2), 29.8 (CH), 29.2 (CH_2), 29.0 (CH_2), 26.5 (CH), 22.6 (CH), 21.6 (CH), 15.3 (CH), 14.13 (CH), 14.06 (CH), 11.5 (CH_2). **ESI-MS** calcd for $C_{27}H_{35}NNaO_2S$ $[M+Na]^+$ 460.23, found: 460.23.

(1S,5R,6S)-6-phenyl-1-((S)-spiro[2.5]octan-1-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane 4n was isolated following the **GP-2** using **1a** (65.0 mg, 0.2 mmol) and **methylenecyclohexane** (384.6 mg, 4.0 mmol) as reagents. Yield **40**% (33.5 mg, 0.079 mmol). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.73 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 7.4 Hz, 2H), 7.25 – 7.11 (m, 3H), 7.08 (d, *J* = 7.3 Hz, 2H), 3.67 (d, *J* = 9.3 Hz, 1H), 3.61 (d, *J* = 9.2 Hz, 1H), 3.23 (dd, *J* = 9.2, 3.9 Hz, 1H), 3.09 (d, *J* = 9.2 Hz, 1H), 2.44 (s, 3H), 2.05 (d, *J* = 4.2 Hz, 1H), 1.69 (t, *J* = 4.0 Hz, 2H), 1.57 – 1.49 (m, 1H), 1.43 – 0.99 (m, 6H), 0.98 – 0.84 (m, 1H), 0.73 (d, *J* = 13.2 Hz, 1H), 0.68 – 0.54 (m, 2H), -0.01 (dd, *J* = 8.6, 4.7 Hz, 1H), -0.30 (t, *J* = 5.1 Hz, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ = 143.5 (Cq), 137.6 (Cq), 133.2 (Cq), 129.6 (2CH), 128.8 (2CH), 127.9 (2CH), 127.7 (2CH), 125.9 (CH), 55.4 (CH_2), 50.4 (CH_2), 37.2 (CH_2), 34.1 (Cq), 31.0 (CH_2), 30.0 (CH), 27.3 (CH), 26.3 (CH_2), 25.7 (CH_2), 25.3 (CH_2), 23.3 (Cq), 22.5 (CH_3), 21.5 (CH), 18.2 (CH_2). **ESI-MS** calcd for $C_{26}H_{31}NNaO_2S$ $[M+Na]^+$ 444.20, found: 444.22.

((1R,2S)-2-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)cyclopropyl)methyl acetate (dr 4:1) 4o was isolated following the **GP-2** using **3a** (65.0 mg, 0.2 mmol) and **allyl acetate** (430 µL, 4.0 mmol) as reagents. White solid. Yield **50**% (42.1 mg, 0.099 mmol). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.71 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.26 – 7.06 (m, 5H), 3.84 – 3.76 (m, 1H), 3.69 (dd, *J* = 9.4, 6.3 Hz, 2H), 3.56 (dd, *J* = 12.1, 6.7 Hz, 1H), 3.27 (dd, *J* = 9.5, 3.8 Hz, 1H), 3.14 (d, *J* = 9.4 Hz, 1H), 2.42 (s, 3H), 2.11 (d, *J* = 4.2 Hz, 1H), 1.93 (s, 3H), 1.77 (t, *J* = 4.0 Hz, 1H), 1.08 – 0.93 (m, 2H), 0.29 (td, *J* = 8.7, 5.6 Hz, 1H), -0.24 (q, *J* = 5.7 Hz, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ = 170.9 (Cq), 143.6 (Cq), 136.8 (Cq), 134.0 (Cq), 129.7 (2CH), 129.0 (2CH), 128.1 (2CH), 127.4 (2CH), 126.2 (CH), 64.2 (CH_2), 54.9 (CH_2), 49.8 (CH_2), 33.0

(Cq), 29.3 (CH), 25.9 (CH), 21.5 (CH_3), 20.9 (CH_3), 15.0 (CH), 14.0 (CH), 10.0 (CH_2). **ESI-MS** calcd for $C_{24}H_{27}NNaO_4S$ $[M+Na]^+$ 448.16, found: 448.17.

butyl 2-((1S,2S)-2-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)cyclopropyl)acetate 4p was isolated following the **GP-2** using **3a** (65.0 mg, 0.2 mmol) and **butyl but-3-enoate** (568 μL, 4.0 mmol) as reagents. Yield **37**% (34.7 mg, 0.074 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.26 – 7.15 (m, 3H), 7.09 (d, *J* = 7.1 Hz, 2H), 4.03 – 3.94 (m, 1H), 3.71 (d, *J* = 9.4 Hz, 1H), 3.65 (d, *J* = 9.4 Hz, 1H), 3.26 (dd, *J* = 9.4, 3.8 Hz, 1H), 3.03 (d, *J* = 9.4 Hz, 1H), 2.43 (s, 3H), 2.11 (d, *J* = 4.2 Hz, 1H), 2.01 (dd, *J* = 16.1, 4.0 Hz, 1H), 1.73 (t, *J* = 4.0 Hz, 1H), 1.64 – 1.51 (m, 2H), 1.44 – 1.28 (m, 2H), 0.99 – 0.84 (m, 5H), 0.33 (td, *J* = 8.7, 5.6 Hz, 1H), -0.33 (q, *J* = 5.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 172.9 (Cq), 143.7 (Cq), 137.0 (Cq), 133.4 (Cq), 129.7 (2CH), 128.9 (2CH), 128.0 (2CH), 127.6 (2CH), 126.2 (CH), 64.4 (CH_2), 55.1 (CH_2), 50.1 (CH_2), 34.0 (CH_2), 33.3 (Cq), 30.7 (CH_2), 29.5 (CH), 26.4 (CH), 21.5 (CH), 19.1 (CH_2), 14.1 (CH), 13.7 (CH), 11.2 (CH), 11.1 (CH_2).

((1R,2S)-2-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)cyclopropyl)methanol 4q was isolated following the **GP-2** using **3a** (65.0 mg, 0.2 mmol) and **allyl alcohol** (270 μL, 4.0 mmol) as reagents. Yield **34**% (26.5 mg, 0.069 mmol). Yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.75 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.11 (m, 5H), 3.72 (d, *J* = 9.3 Hz, 1H), 3.68 (d, *J* = 9.3 Hz, 1H), 3.22 – 3.15 (m, 4H), 2.47 (s, 3H), 2.20 (d, *J* = 4.2 Hz, 1H), 1.75 (q, *J* = 3.6 Hz, 1H), 1.07 – 0.87 (m, 2H), 0.38 – 0.25 (m, 1H), -0.24 (q, *J* = 5.6 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 143.6 (Cq), 137.1 (Cq), 133.3 (Cq), 129.6 (2CH), 128.8 (2CH), 128.1 (2CH), 127.7 (2CH), 126.2 (CH), 62.5 (CH_2), 55.2 (CH_2), 50.0 (CH_2), 33.3 (Cq), 29.6 (CH), 26.6 (CH), 21.6 (CH_3), 17.5 (CH), 14.9 (CH), 9.6 (CH_2). **ESI-MS** calcd for $C_{22}H_{25}NNaO_3S$ $[M+Na]^+$ 406.15, found: 406.18.

(S)-3-(((1R,2S)-2-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)cyclopropyl)methoxy)propane-1,2-diol and **(R)-3-(((1R,2S)-2-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)cyclopropyl)methoxy)propane-1,2-**

diol 4r were isolated as a mixture of diastereomers following the **GP-2** using **1a** (65.0 mg, 0.2 mmol) and **3-(allyloxy)propane-1,2-diol** (495 μL, 4.0 mmol) as reagents. Yield **36**% (32.7 mg, 0.071 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, $2H_A$, $2H_B$), 7.37 (d, *J* = 7.9 Hz, $2H_A$, $2H_B$), 7.30 – 7.21 (m, $3H_A$, $3H_B$), 7.18 – 7.05 (m, $2H_A$, $2H_B$), 3.86 – 3.78 (m, $1H_A$, $1H_B$), 3.74 – 3.56 (m, $8H_A$, $8H_B$), 3.43 – 3.26 (m, $8H_A$, $8H_B$), 3.23 – 3.00 (m, $4H_A$, $4H_B$), 2.46 (s, $3H_B$), 2.43 (s, $3H_A$), 2.00 (t, *J* = 3.4 Hz, $1H_A$, $1H_B$), 1.76 (t, *J* = 4.1 Hz, $1H_A$, $1H_B$), 0.99 (ddt, *J* = 12.2, 8.2, 6.4 Hz, $1H_A$, $1H_B$), 0.32 (td, *J* = 8.6, 5.4 Hz, $1H_A$, $1H_B$), -0.24 (qd, *J* = 5.7, 1.2 Hz, $1H_A$, $1H_B$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.79 (Cq), 143.74 (Cq), 137.01 (Cq), 136.90 (Cq), 134.03 (Cq), 133.96 (Cq), 129.75 (4CH), 128.93 (4CH), 128.05 (4CH), 127.59 (2CH), 127.56 (2CH), 126.17 (2CH), 72.15 (CH_2), 72.10 (CH_2), 71.47 (CH_2), 71.40 (CH_2), 70.56 (CH), 70.54 (CH), 64.01 (CH_2), 63.79 (CH_2), 54.92 (CH_2), 49.89 (CH_2), 33.43 (Cq), 33.42 (Cq), 29.72 (CH), 26.24 (CH), 26.23 (CH), 21.57 (CH_3), 14.96 (CH), 14.94 (CH), 14.51 (CH), 14.50 (CH), 10.08 (CH_2), 10.05 (CH_2). **ESI-MS** calcd for $C_{25}H_{31}NNaO_5S$ $[M+Na]^+$ 480.18, found: 480.19.

4-methyl-N-(((1R,2S)-2-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)cyclopropyl)methyl) benzenesulfonamide dr 4:1 4s was isolated following the **GP-2** using **1a** (65.4 mg, 0.2 mmol) and **N-allyl-4-methylbenzenesulfonamide** (787.0 mg, 4.0 mmol) as reagents. White solid. Yield **44**% (44.1 mg, 0.082 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.27 (m, 3H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 7.2 Hz, 2H), 4.11 (brs, 1H), 3.63 (d, *J* = 9.5 Hz, 1H), 3.57 (d, *J* = 9.5 Hz, 1H), 3.06 (dd, *J* = 9.4, 3.8 Hz, 1H), 2.92 (d, *J* = 9.4 Hz, 1H), 2.78 – 2.65 (m, 1H), 2.46 (s, 6H), 2.32 – 2.20 (m, 1H), 2.07 (d, *J* = 4.2 Hz, 1H), 1.54 (t, *J* = 3.9 Hz, 1H), 0.96 (q, *J* = 8.4 Hz, 1H), 0.78 – 0.64 (m, 1H), 0.24 (td, *J* = 8.6, 5.7 Hz, 1H), -0.41 (q, *J* = 5.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.1 (Cq), 143.6 (Cq), 136.8 (Cq), 136.7 (Cq), 133.1 (Cq), 129.9 (CH_2), 129.7 (2CH), 128.6 (2CH), 128.2 (2CH), 127.5 (2CH), 127.0 (2CH), 126.3 (CH), 55.1 (CH_2), 49.8 (CH_2), 43.2 (CH_2), 32.9 (Cq), 29.6 (CH), 26.8 (CH), 21.63 (CH_3), 21.59 (CH_3), 15.5 (CH), 14.8 (CH), 10.0 (CH_2). **ESI-MS** calcd for $C_{29}H_{32}N_2NaO_4S_2$ $[M+Na]^+$ 559.17 found: 559.20.

2-((1S,2S)-2-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)cyclopropyl)acetonitrile 4t was isolated following the **GP-2** using **1a** (65.0 mg, 0.2 mmol) and **allyl cyanide** (322 μL, 4.0 mmol) as reagents. White solid. Yield **46**% (36.2 mg, 0.079 mmol). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.18 (m, 3H), 7.08 (d, *J* = 7.2 Hz, 2H), 3.74 (d, *J* = 9.5 Hz, 1H), 3.69 (d, *J* = 9.6 Hz, 1H), 3.21 (dd, *J* = 9.5, 3.8 Hz, 1H), 3.01 (d, *J* = 9.5 Hz, 1H), 2.46 (s, 3H), 2.22 (d, *J* = 4.2 Hz, 1H), 1.93 (dd, *J* = 17.2, 5.8 Hz, 1H), 1.77 (t, *J* = 3.5 Hz, 1H), 1.67 (dd, *J* = 17.3, 8.6 Hz, 1H), 1.12 – 1.02 (m, 1H), 0.91 (tdd, *J* = 8.4, 5.7, 2.7 Hz, 1H), 0.48 (td, *J* = 8.8, 6.0 Hz, 1H), -0.20 (q, *J* = 5.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 144.0 (Cq), 136.5 (Cq), 133.0 (Cq), 129.8 (2CH), 128.6 (2CH), 128.2 (2CH), 127.6 (2CH), 126.4 (CH), 118.8 (Cq), 55.1 (CH_2), 50.0 (CH_2), 32.6 (Cq), 29.7 (CH), 26.9 (CH), 21.6 (CH_3), 17.1 (CH), 15.4 (CH), 11.5 (CH_2), 11.3 (CH_2). **ESI-MS** calcd for $C_{23}H_{24}N_2NaO_2S$ $[M+Na]^+$ 415.15, found: 415.17.

(1S,5R,6S)-6-phenyl-3-tosyl-1-((1S,2R)-2-((trimethylsilyl)methyl)cyclopropyl)-3-azabicyclo[3.1.0]hexane 4u was isolated following the **GP-2** using **1a** (65.0 mg, 0.2 mmol) and **allyltrimethylsilane** (644 μL, 4.0 mmol) as reagents. Yield **31**% (27.3 mg, 0.062 mmol). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.73 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.04 (m, 5H), 3.71 (d, *J* = 9.2 Hz, 1H), 3.65 (d, *J* = 9.0 Hz, 1H), 3.22 – 3.10 (m, 2H), 2.43 (s, 3H), 2.19 (d, *J* = 4.2 Hz, 1H), 1.63 (t, *J* = 4.0 Hz, 1H), 0.79 – 0.69 (m, 1H), 0.60 – 0.43 (m, 1H), 0.30 – 0.14 (m, 2H), -0.13 (d, *J* = 0.7 Hz, 9H), -0.51 (dd, *J* = 14.2, 12.2 Hz, 1H), -0.63 (q, *J* = 5.4 Hz, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ = 143.5 (Cq), 137.6 (Cq), 132.6 (Cq), 129.6 (2CH), 129.0 (2CH), 127.9 (2CH), 127.8 (2CH), 125.9 (CH), 55.2 (CH_2), 50.4 (CH_2), 34.1 (Cq), 29.4 (CH), 26.4 (CH), 21.6 (CH_3), 16.0 (CH_2), 13.7 (CH_2), 12.9 (CH), 10.5 (CH), -1.6 ($3CH_3$). **ESI-MS** calcd for $C_{25}H_{33}NNaO_2SSi$ $[M+Na]^+$ 462.19, found: 461.93.

((1R,2S)-2-((1S,5R,6S)-6-phenyl-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)cyclopropyl-3-d)methanol *d*$_1$4q was isolated following the **GP-2** using **1a** (65.0 mg, 0.2 mmol) and **(Z)-prop-2-en-3-d-1-ol** (278 μL, 4.0 mmol) as reagents. Yield **37**% (28.7 mg, 0.074 mmol). Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 2H), 7.38 – 7.09 (m, 7H), 3.75 – 3.57 (m, 2H), 3.30 – 3.13 (m, 4H), 2.45 (s, 3H), 2.17 (dd, *J* = 9.0, 4.2 Hz, 1H), 1.72 (t, *J* = 3.6 Hz, 1H), 1.03 – 0.84 (m, 1.81H), 0.33 – 0.23 (m, 0.35H), -0.26 (t, *J*

= 5.7 Hz, 0.32H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.6 (Cq), 137.1 (Cq), 133.3 (Cq), 129.6 (2CH), 128.8 (2CH), 128.1 (2CH), 127.7 (2CH), 126.2 (CH), 62.5 (CH_2), 55.2 (CH_2), 50.0 (CH_2), 33.3 (Cq), 29.6 (CH), 26.6 (CH), 21.6 (CH_3), 17.41 (d, *J* = 9.6 Hz, CH), 14.76 (d, *J* = 9.2 Hz, CH), 9.5 (m, CHD).

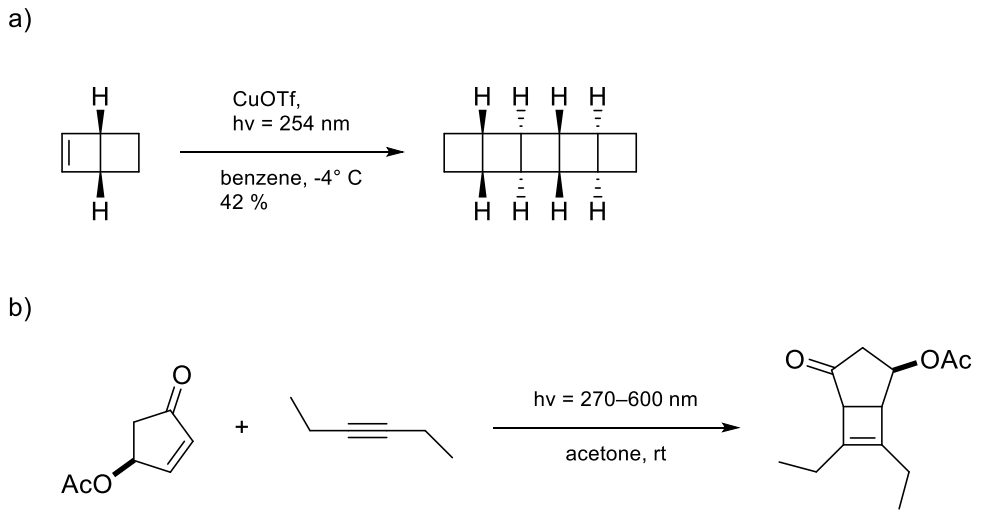
(Z)-3-(1-phenylbut-3-en-1-yl)-4-((phenylselanyl)methylene)-1-tosylpyrrolidine and **(E)-3-(1-phenylbut-3-en-1-yl)-4-((phenylselanyl)methylene)-1-tosylpyrrolidine** were isolated following the **GP-2** using **1a** (62.4 mg, 0.19 mmol) and **allyl(phenyl)selane** (735 mg, 4.0 mmol) as reagents. Yield **37**% (28.7 mg, 0.074 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, $2H_A$), 7.67 (d, *J* = 8.2 Hz, $2H_B$), 7.47 – 7.03 (m, $12H_A$, $12H_B$), 6.45 (s, $1H_B$), 5.85 – 5.77 (m, $1H_A$), 5.62 – 5.44 (m, $1H_A$, $1H_B$), 4.98 – 4.83 (m, $2H_A$, $2H_B$), 3.85 – 3.70 (m, $2H_A$, $2H_B$), 3.49 – 3.38 (m, $2H_A$, $2H_B$), 3.04 – 2.95 (m, $1H_A$), 2.94 – 2.87 (m, $1H_B$), 2.79 – 2.70 (m, $1H_A$, $1H_B$), 2.51 – 2.29 (m, $5H_A$, $5H_B$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.8, 143.6, 142.3, 142.0, 141.7, 141.5, 136.1, 135.8, 132.9, 132.6, 131.9, 131.7, 131.3, 130.5, 130.4, 129.8, 129.7, 129.4, 129.2, 128.6, 128.5, 128.5, 128.4, 127.9, 127.8, 127.0, 126.8, 126.8, 116.7, 116.6, 114.7, 113.9, 52.3, 51.6, 51.6, 51.2, 50.7, 49.8, 48.3, 47.3, 37.8, 37.3, 21.6, 21.6. **^{77}Se NMR** (76 MHz, $CDCl_3$) δ 343.88.

3 Orthogonal synthesis of 3.2.0 bicycles *via* 2+2 cycloaddition promoted by visible light

From this chapter: Andrea Serafino, Davide Balestri, Luciano Marchiò, Max Malacria, Etienne Derat, Giovanni Maestri. *Org. Lett.* **2020**, 22, 16, 6354–6359.

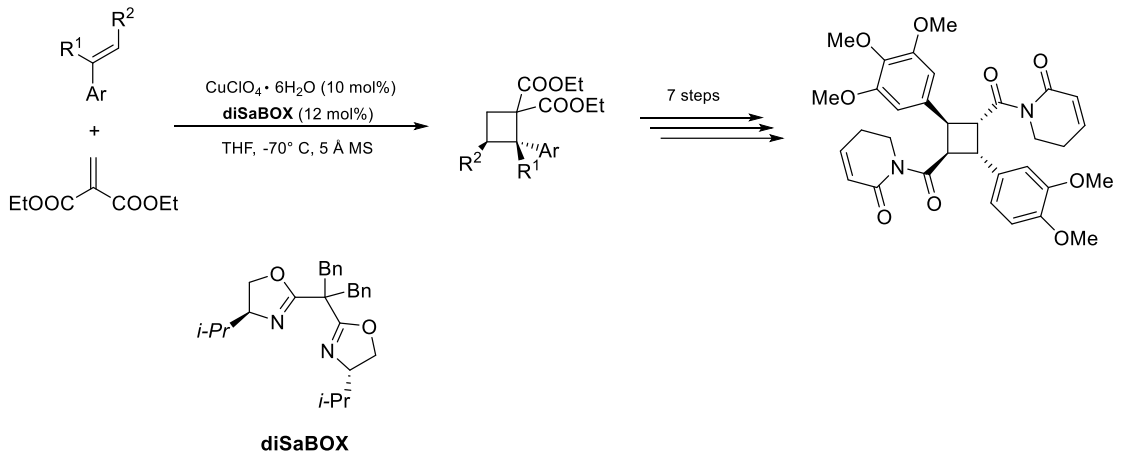
3.1 Introduction

Cyclobutanes are important structural motif found in numerous organic intermediates[46] and natural products[47]. The first synthesis of cyclobutene was reported by Willstätter and Bruce in 1907[48]. In the following years, more and more approaches, including cyclization of dihalobutane[49] and double alkylation of malonic esters[50], were developed in order to obtain cyclobutanes. However, the most simple and useful protocol for the preparation of 4-membered rings is the [2+2] cycloaddition. A myriad of different unsaturations were successfully employed in the synthesis of polysubstituted cyclobutanes and cyclobutenes including alkenes, alkynes, dienes, enones, acrylates and ketenes. Depending on the unsaturation involved in the cycloaddition, light, heat, transition metal catalysts or Lewis acids can lead to cyclobutene target. An interesting example of 2+2 cycloaddition between two inactivated alkene moieties can be found in the total synthesis of a ladderane phospholipid by Burns and co-workers. The [5]-ladderane core was obtained via 2+2 cycloaddition of two bicyclohexenes in the presence of copper (I) triflate and UV radition (254 nm) in benzene at -4° C.[51] (Scheme 19, a)). Quantum yield studies support the hypothesis on the formation of a 2:1 olefine-copper complex that, after excitation by UV radiation, immediately collapse to the product[52]. In the first total synthesis of (±)-Hippolachnin A, the Carreira group synthetized the 3.2.0 bicyclic core of the target molecule via photoinduced enone-alkene 2+2 cycloaddition[53] (Scheme 19, b)).



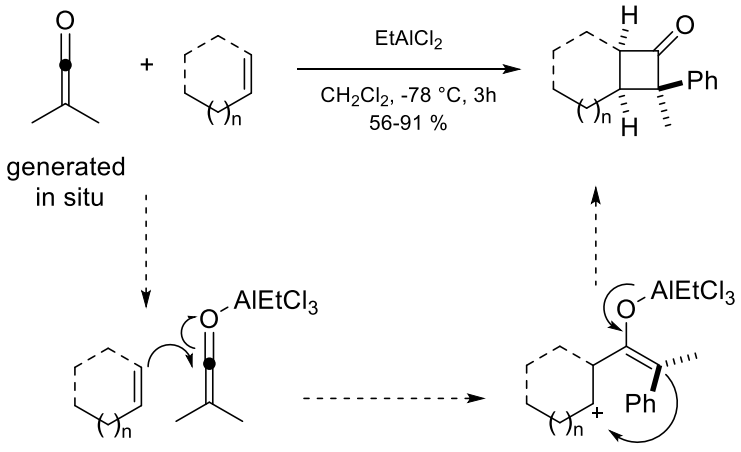
Scheme 19 selected examples of: a) challenging 2+2 photocycloaddition promoted by Cu(I) and UV. radiation. b) 2+2 photocycloaddition triggered by direct enone activation

The presence of two conjugated unsaturations of enones paves the way to the cycloaddition catalysed by Lewis acid[54–58]. Among many cited examples, the enantioselective 2+2 cycloaddition that Xie and Tang optimized for the total synthesis of (+) piperarborenine B is remarkable[59] (Scheme 20).



Scheme 20 selected example of enantioselective 2+2 cycloaddition promoted by Lewis acid.

In 2013 Brown proved the potential of Lewis acid approach publishing the first ketene-alkene 2+2 cycloaddition catalysed by ethylaluminum dichloride. This innovative method, in addition to high yield and stereoselectivity, shows inverse selectivity compared to traditional thermal approaches [affording precious substituted cyclobutanones[60] (Scheme 21).



Scheme 21 selected example of ketene-alkene 2+2 cycloaddition promoted by Lewis acid.

Since Dorothy Hodgkin has solved the structure of penicillin in 1945, [3.2.0] and [n.2.0] bicyclic structures gained increasing attention because of their abundance in biologically active molecules (Figure 9). Obviously, the presence of a 4-membered ring makes the 2+2 intramolecular cycloaddition the main method for the preparation of these compounds.

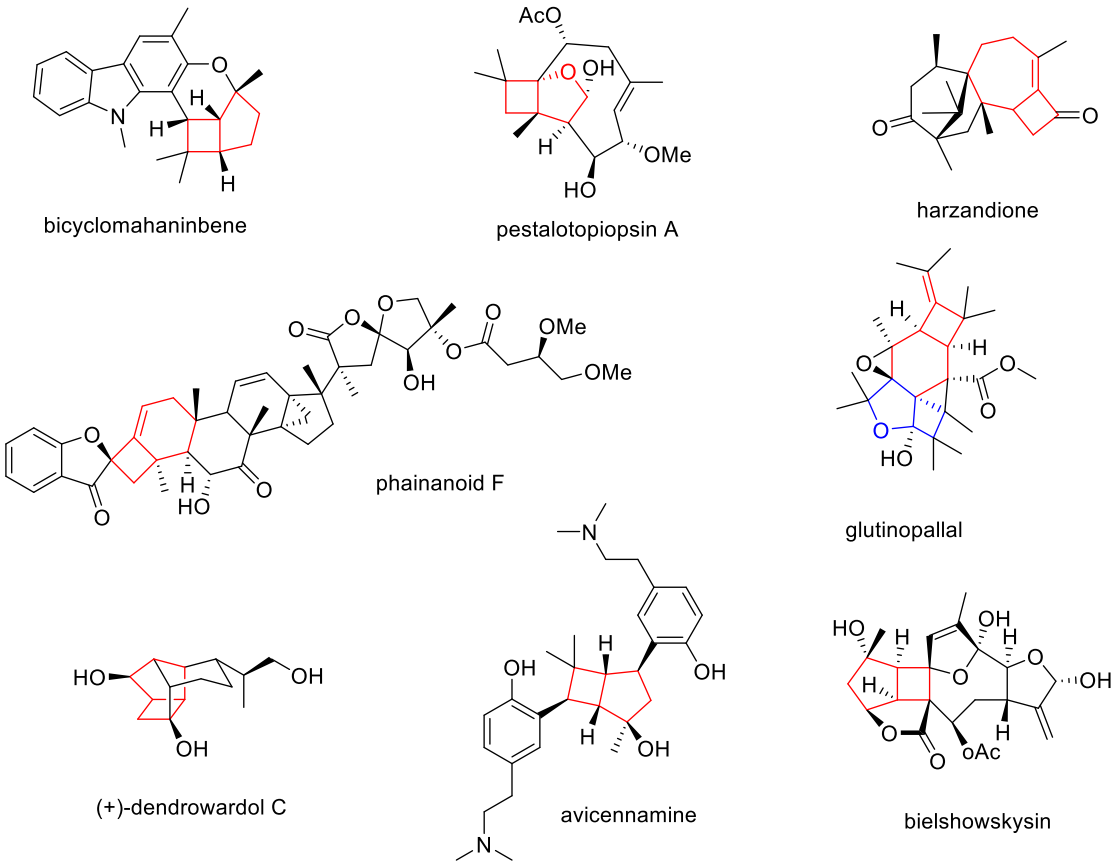
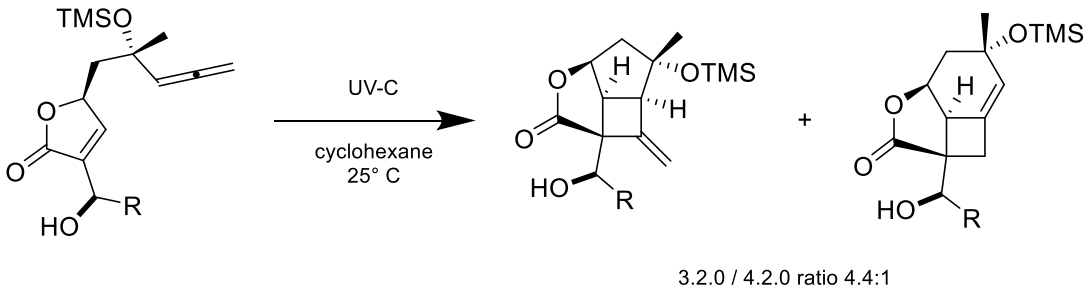


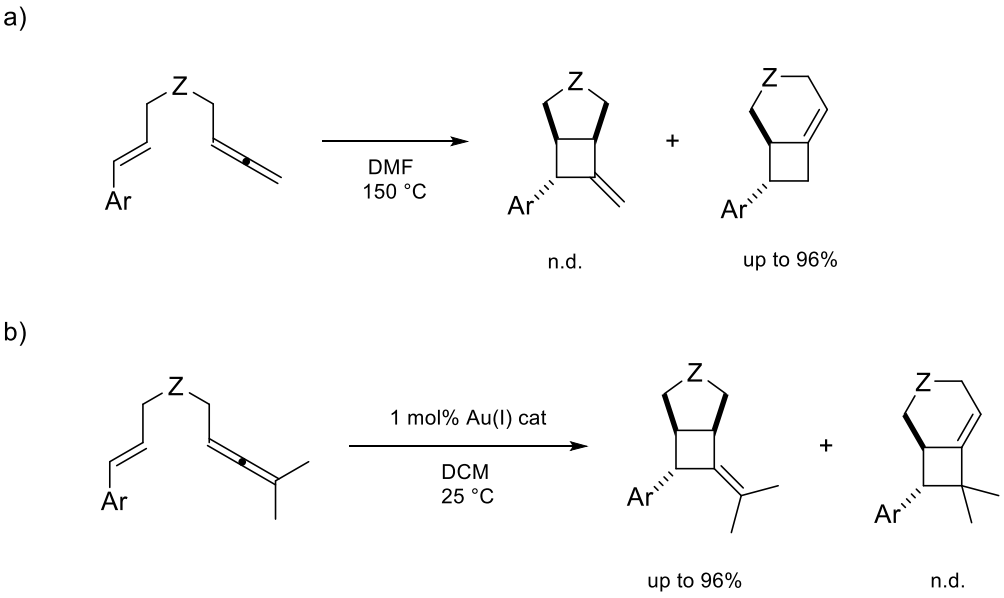
Figure 9 selected examples of natural products containing n.2.0. bicycles.

Due to the increasing interest toward cumulated double bonds of allene motif[61–63], the alkene-allene combination recently gained attention in the synthesis of vinylidene ciclobutanes. If on the one hand the use of allene partners in the 2+2 cycloaddition allows to obtain complex vinylidene cyclobutene structures with high atom economy, on the other it brings to light a challenging regiochemical problem. This issue is shown in the synthesis of Bielschowskysin, in which a mixture of isomers was observed in the key annulation promoted by UV-C light[64] (Scheme 22).



Scheme 22 example of low regiochemical in a 2+2 cycloaddition that involves allene moiety.

However, in some cases complete regiochemical control can be observed. Thermal activation of 1,7 enallenes afforded 4.2.0 bicyclic structures with high regio and stereochemical control but required harsh condition[65] (Scheme 23, a)). Cationic gold(I) complexes can smoothly activate analogous substrates at room temperature, leading to 3.2.0 products instead. However, a selective reaction requires that the gold catalyst could discriminate between the two cumulated double bonds, limiting the method to trisubstituted allenes[66] (Scheme 23, b)).



Scheme 23 selected example of regioselective 2+2 cycloaddition using allene moiety.

Herein we reported a more general tool for the preparation of 3.2.0 bicyclic structure using visible light-induced cyclization of enallenes.

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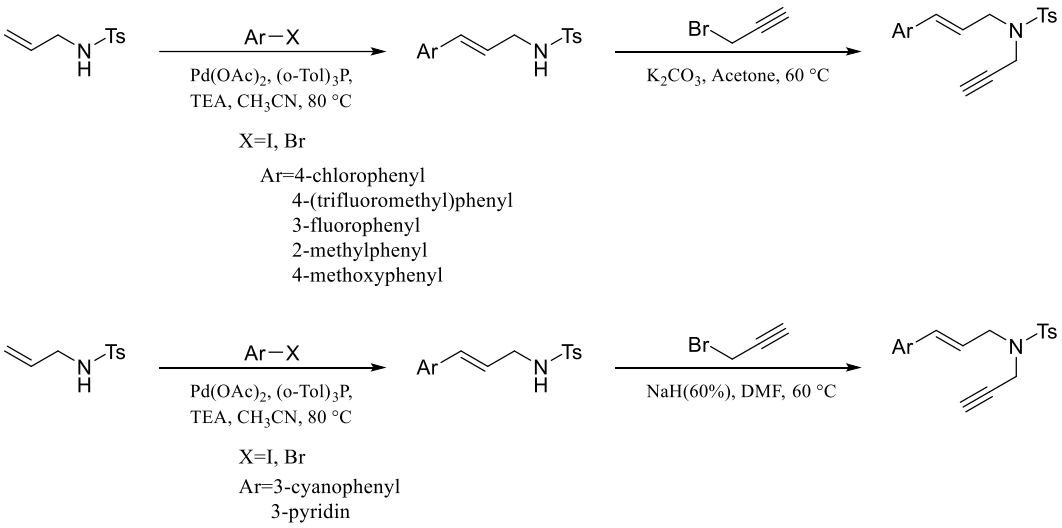
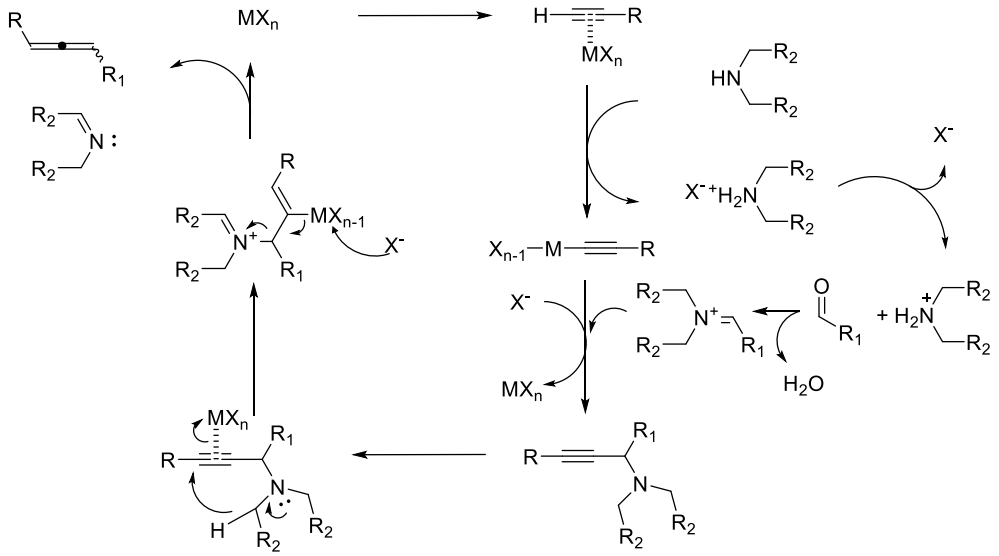
3.2 Results and discussion

The preparation of enallenes has requested an intensive synthetic work. Starting from tosyl allylamine we prepared the corresponding cinnamyl tosylamides using reported Heck coupling[67]. The following propargylation afforded 1,6 enynes (Scheme 24).



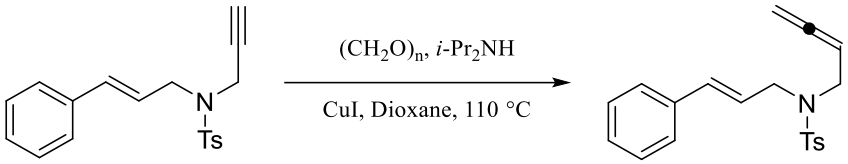
Scheme 24 Synthesis of 1,6 enynes.

The preparation of monosubstituted 1,7 enallenes preceded via Crabbè-Ma homologation[68]. The reaction originally developed by Pierre Crabbè and extended by Shengming Ma converts terminal alkynes in corresponding allenes using a soft Lewis acid (Cu^{+}, Zn^{2+}, Cd^{2+}) and an activated iminium ion (Scheme 25). Several modified procedures were employed.



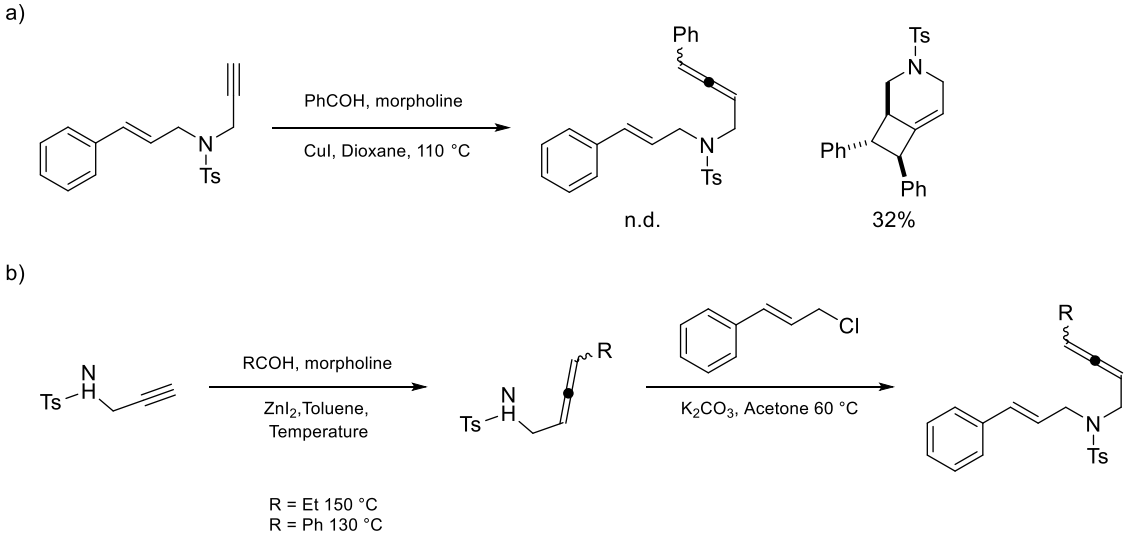
Scheme 25 Proposed mechanism of allenation of terminal alkynes with aldehydes.

For monosubstituted 1,7 allenamides, copper catalyzed homologation was used[69] employing the corresponding 1,6 enynes, paraformaldehyde and diisopropylamine (Scheme 26).



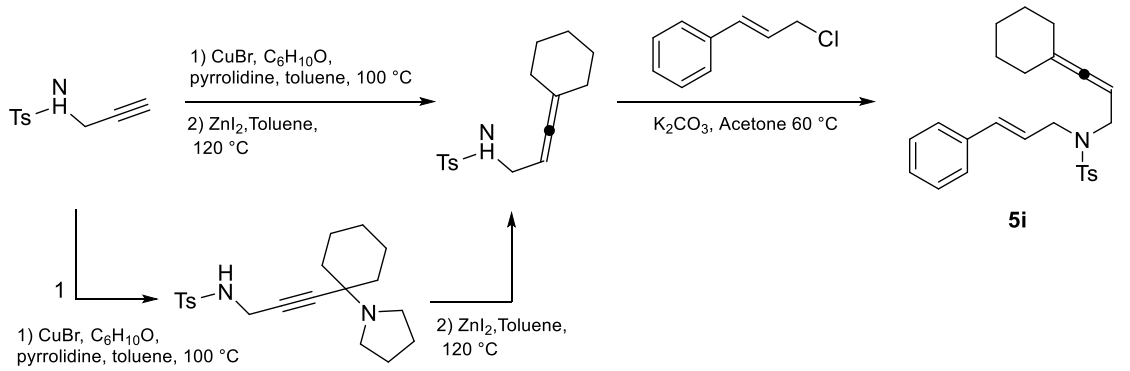
Scheme 26 allenation of terminal alkyne via copper catalyzed crabbe' homologation.

During the preparation of 1,7 enallenes in which a disubstituted allene moiety was present, we used the procedure developed for these substrates, which utilized zinc (II) iodide, morpholine and an alkyl/aryl aldehyde[70]. Unfortunately, 1,7 enallenes have proved unstable under the reaction condition affording bicycles **6'l** as reported in leterature[71] (Scheme 27, a)). We therefore modified the synthetic plan. Using the same homologation procedure, we prepared 1,3-disubstituted allenes from tosyl propargylamine. The following nucleophilic substitution enabled us to access substrates with disubstituted allenes under milder condition (Scheme 27, b)).



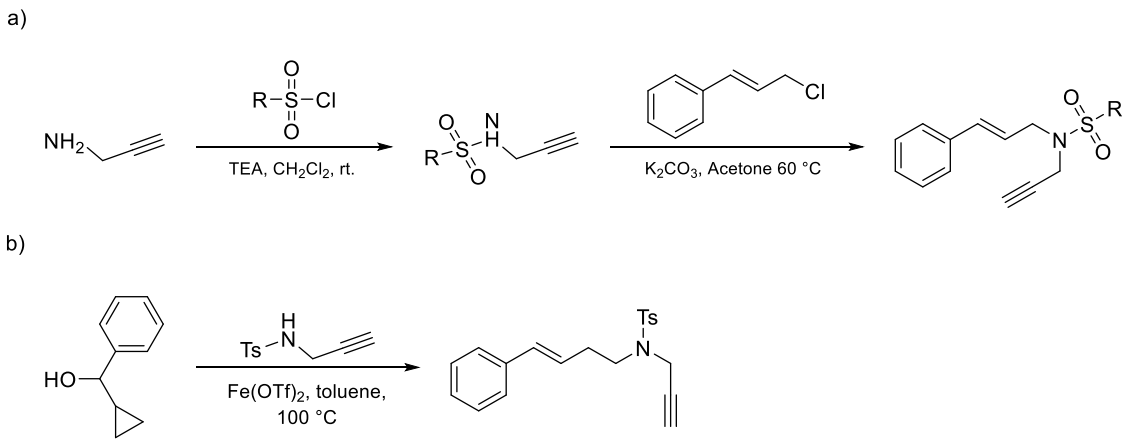
Scheme 27 a) example of thermal 2+2 cycloaddition. b) new synthetic plan for the preparation of enallenes 5.

The extremely low reactivity of ketones required different procedure. 1,3-trisubstituted allenes could be prepared from terminal alkynes and ketones using Cadmium (II) iodide[72]. However, the use of Cadmium salt was not immune to hazards. For this reason, a safer procedure was employed. This approach divided the synthesis in 2 steps. In the first, tosylpropargylamide react with iminium cation in presence of Cu(I) affording the corresponding propargylamine. In the second one, the latter was converted to 1,3 trisubstituted allene[73]. The following nucleophilic substitution afforded enallene **5i** (Scheme 28).



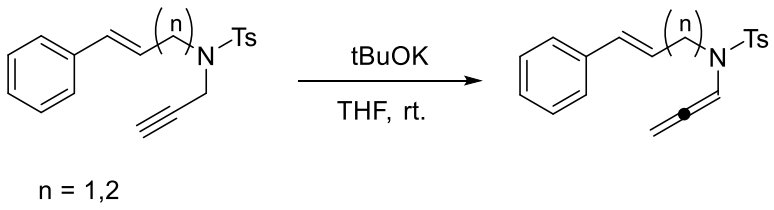
Scheme 28 synthesis of trisubstituted enallene 5i.

The preparation of 1,6 enallenes was considerably simpler. Aryl substituted 1,6 enynes were obtained as above descripted. Various sulfonyl substituted enynes were obtained by sulfonylation of propargylamine followed by nucleophilic substitution (Scheme 29, a)). 1,7 enyne was achieved via cationic cyclopropane opening followed by nucleophilic addition using iron (II) triflate as catalyst (Scheme 29, b)).



Scheme 29 a) Synthesis of sulfonyl substituted 1,6 enynes. B) Synthesis 1,7 enyne.

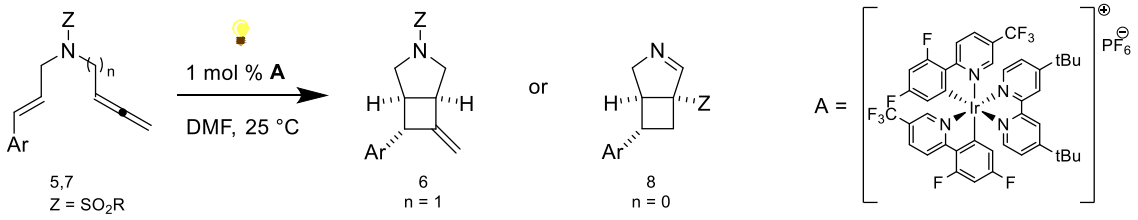
The corresponding 1,6 enallenes were obtained by isomerization using potassium tert-butoxide (Scheme 30).



n = 1,2

scheme 30 synthesis of 1,6 enallenes

On the base of the important work in the field of intramolecular [2+2] cycloaddition trigger by activation of alkenes via eT[27,28,74–77], we focused our attention on the reactivity of 1,n enallenes. This strategy is complementary to thermal and organometallic methodologies to obtain vinylidencyclobutanes. The activation of 1,7 enallenes **5a** lead to 3.2.0 bicyclic unit **6a**, which have three contiguous stereocenter, with high stereo and regiochemical control. Under the same condition, 1,6 enallenes **7a** deliver an original 3.2.0 bicyclic unit **8a** with total stereo and regiochemical control in which a formal 1,3-sigmatropic rearrangement of the sulfonyl group[78–80] creates a strongly congested tetrasubstituted carbon on the headbridging position and an imine functional group (Scheme 31)



Scheme 31 orthogonal synthesis of 3.2.0 bicyclic units.

After a short screening of reaction condition, we found that the popular photocatalyst **A** and dimethylformamide (DMF) are the more suitable combination for this reaction. The optimized reaction was carried out in presence of 1 mol % of **PC4** on a 0.2 mmol scale under nitrogen atmosphere in DMF (0.05 M). The mixture was placed in a nuclear magnetic resonance (NMR) tube and irradiated with a light-emitted diode (LED) strip (spectral window from 350 to 750 nm) at 25 °C keeping the temperature with the aid of an oil bath. **6a** was isolated in 80% yield under the above-mentioned condition and its structure was confirmed by X-ray analysis (Figure 10).

With the optimized condition in hand, we prepared a library of 1,7 enallenes starting from the corresponding 1,6 enynes via homologation of a terminal alkyne[81]. The styryl arm was enriched with various electron withdrawing group included redox-sensitive cyano and pyridine, getting the corresponding products in moderate to good yield (**6a-f** 53-67 %). In the same way electron donating groups were well tolerated (**6g-h** 80 and 63 respectively), although the diasterocontrol was lower using **5g** (dr 1:6). The presence of oxygen instead of sulfonamide

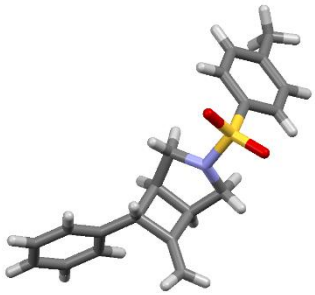


Figure 10 ORTEP of 6a.

lead to product **6j** (49% yield). Turning the attention on the allene fragment, complete regiochemical control was observed using trisubstituted allene **5i** (**6i** 66% yield). A disubstituted allene followed the same line, although the product was recovered in a mixture of E/Z isomers (5:1). The substrate **5l**, which had phenyl allene and styryl arm, show a loss of regiochemical control. We observed two different products depending on the double bond of allene that was involved in the cycloaddition. Together with **6l** (35% yield, E/Z 1:1 mixture) we recovered **6'l** (35 %), a 4.2.0 bicyclic unit with three contiguous stereocenters whose structure was confirmed by XRD analysis (Figure 11). This result showed that functionalization of distal unsaturation of allene was possible under descripted condition (scheme 32).

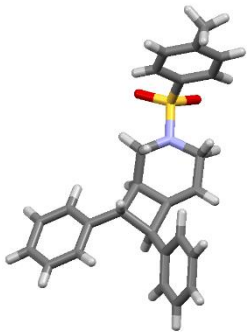
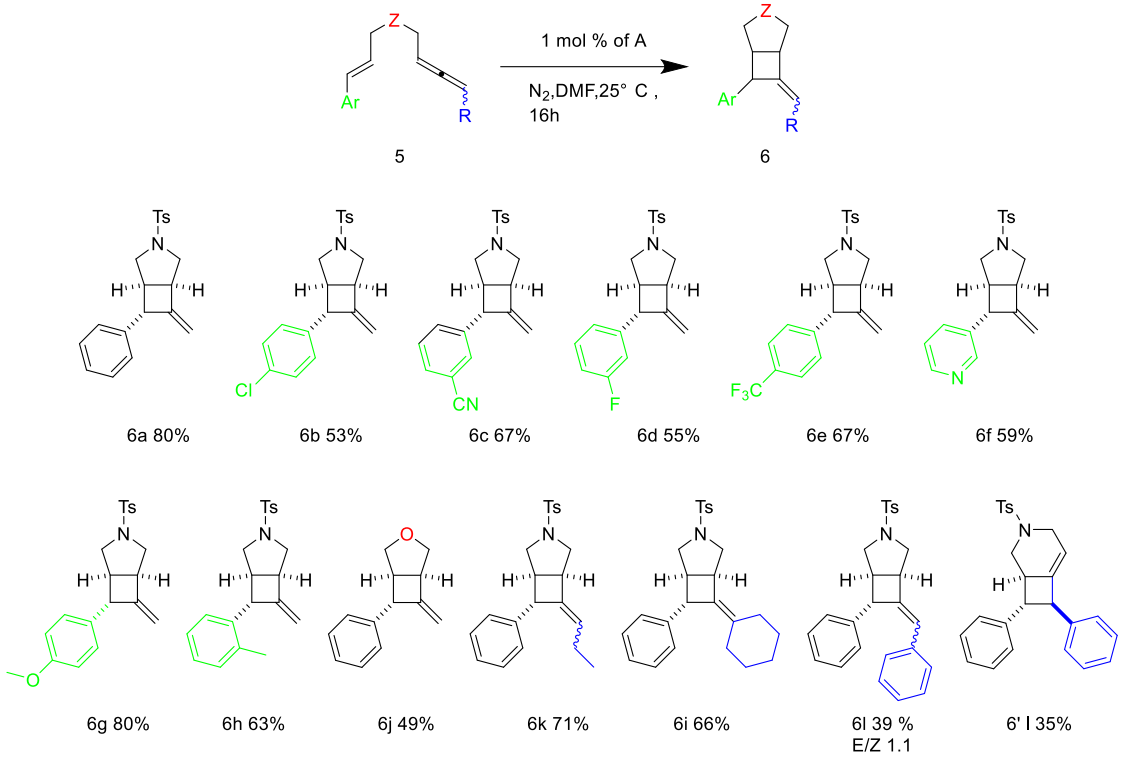
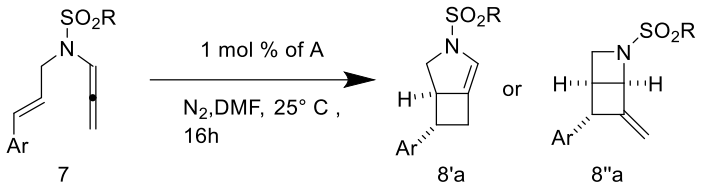


Figure 11 ORTEP of 6'l.



Scheme 32 Scope of vinylidencyclobutanes 6.

We thus thought to elicit a distal-selective variant of the reaction by preparing 1,6-enallenes, reasoning that the formation of a 3.2.0 product **8'a** would have been favoured over that of the corresponding 2.2.0 product **8''a** (scheme 33). Enallenes **7** were prepared via isomerization from the corresponding enynes.



Scheme 33 expected products from the reaction of enallenamide **7.**

Isolation of a 3.2.0 unit partially confirm our hypothesis, but X-ray analysis revealed that its structure was different from the expected one (namely **8'**). Sulfonamide activation and formal 1,3-sigmatropic rearrangement of sulfonyl group took place[78–80], eventually delivering bicyclic imine (**8a**, 59%) as a single diastereomer (Figure 12). To the best of our knowledge, this reactivity is unprecedent in sequence promoted by visible light[82]. We therefore tested its generality. The method could be extended to different styryl partners with electron donating groups (**8b-c** 53-58%) that work better than electron withdrawing ones (**8d-e** 31-38%). The tosyl group could be replaced with mesyl one without significantly affecting the yield (**8f** 49-55%). Similarly, various arylsulfonyl groups were employed, including bulking mesitylene and naphthalene groups. The variation was generally well tolerated by the method, with the only exception of nosyl derivative, which afforded the corresponding product in 27% yield. A longer tether enabled us to access a tetrahydropyridine unit, albeit with a moderate yield (**8m**, 26%) (Scheme 34).

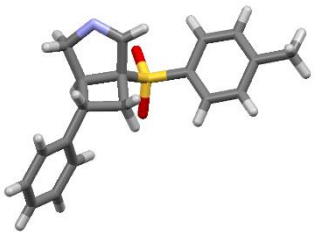
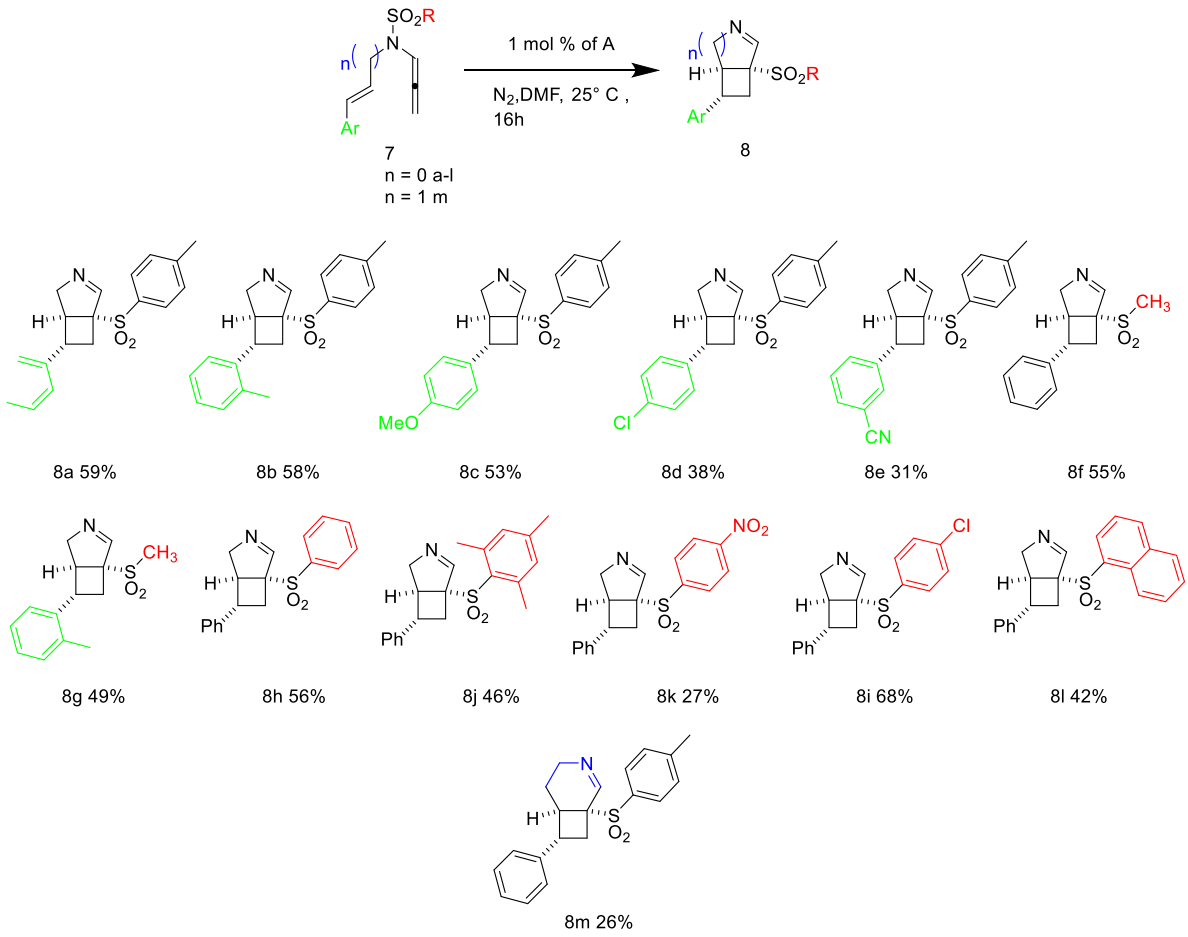
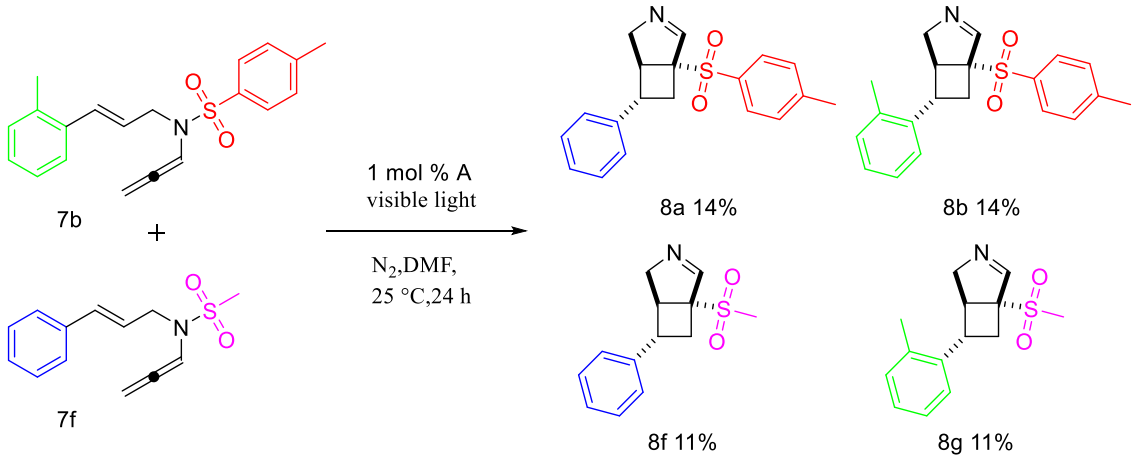


Figure 12 ORTEP of 8a.



Scheme 34 Scope of 3.2.0 heterobicycles **8.**

We then tried to prove whether the sulfonyl fragmentation/recombination occurred through either a uni- or a multimolecular pathway. We performed an experiment using a 1:1 mixture of allenes **7b** and **7f** under optimized conditions (Scheme 35). The analysis of the crude product by NMR clearly shows the presence of four products (Figure13). After chromatography, we obtained two fractions, each of which contains equimolar amount of two product with the same sulfonyl group. This result shows that the rearrangement took place through a multimolecular process.



Scheme 35 double tagging experiment.

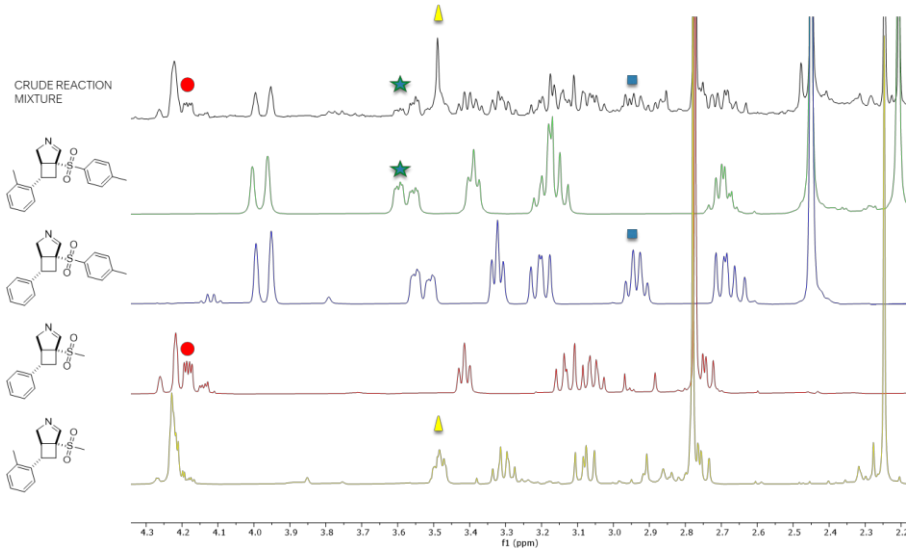
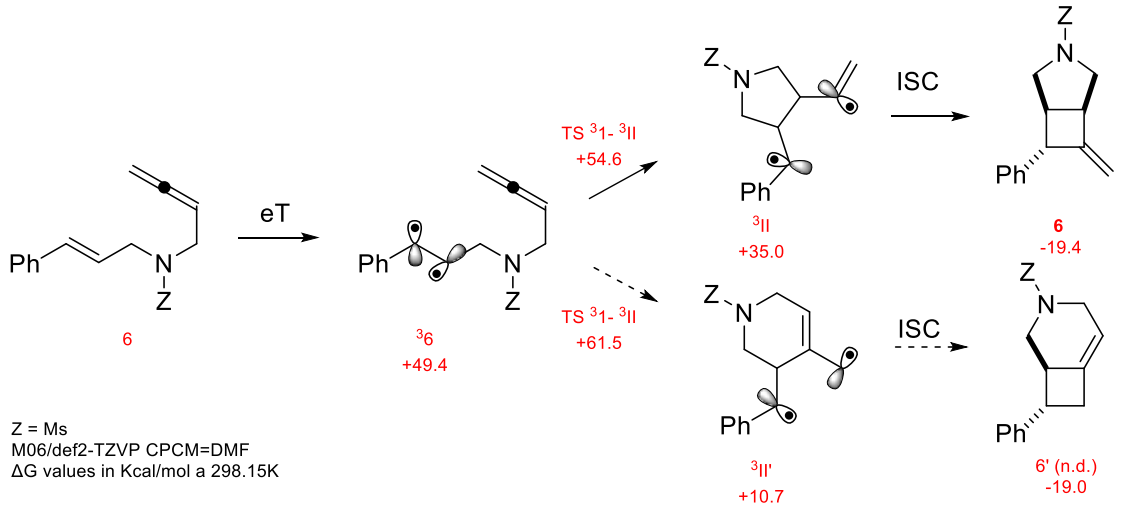


Figure 13 spectrum of crude of double tagging experiment compared with pure compounds 8.

Based on literature studies and experimental/computational studies, we propose the rationale presented below to account for the present complementary cyclization of enallenes. Monosubstituted allenes have triplet energies that do not match that of the iridium complex. Their redox potentials are beyond those accessible using the present catalyst and visible light[28]. The oxidation of styryl fragments, especially those with electron-withdrawing substituents, follow suit[28,83]. On the contrary, the triplet state of the iridium catalyst could activate the vinylarene arm of substrates through an energy transfer (eT) process[28,83]. This correlates with the absence of reactivity observed by replacing the photocatalyst with species that have triplet energies unable to activate β-styryl units, such as the popular $Ru(bpy)_3^{2+}$ complex. Upon eT, intermediate ^{3}**5** can then evolve through two different pathways, forming either a six- or a five-membered ring (^{3}**II′** and ^{3}**II**, respectively). The latter cyclization prevails, enabling the formation of vinylidenecyclobutane **6** upon intersystem crossing (ISC). According to density functional theory (DFT) modeling, this stems from both an easier transition state (TS) and the least stable exergonic intermediate (ΔΔG of −6.9 and +24.3 kcal/mol, respectively, at the M06/def2-TZVP level using DMF as an implicit solvent) (Scheme 36).

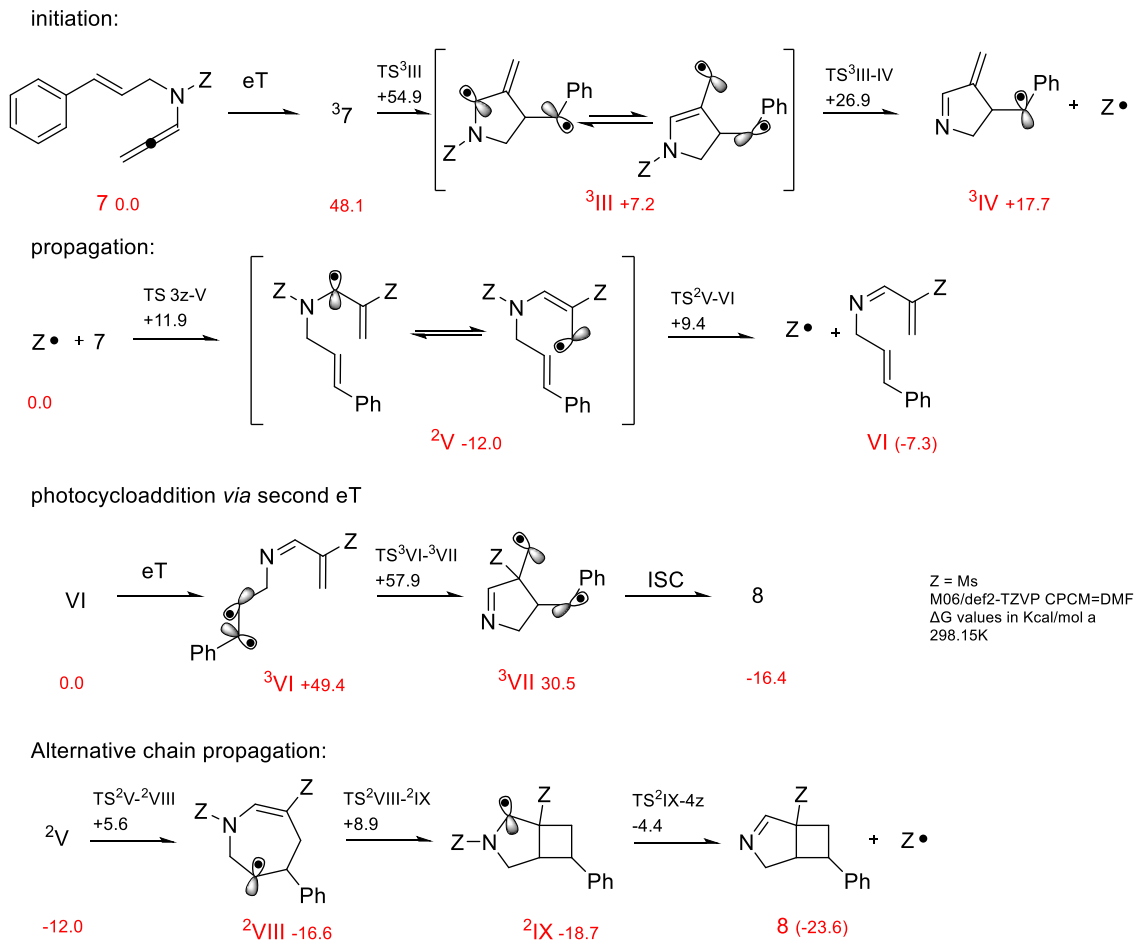


Scheme 36 proposed reaction mechanism for 1,7 enallenes.

Analogous activation of the 1,6-enallene gives triplet ^{3}**7**, for which steric factors disfavour the 4-*exo* cyclization that would have led to a 2.2.0 bicycle. A 5-*exo* cyclization led to intermediate ^{3}**III** through a low barrier (ΔG of +6.8 kcal/mol). The spin density of the ^{3}III is evenly spread, with a slightly preference for the secondary carbon. The ortogonality of the two mono-occupied molecular orbitals in ^{3}**III** probably disfavours the cyclization that would lead to product **8'**. However, the N-S bond length in intermediate

^{3}**III** is slightly longer than that observed in ^{3}**5**. That makes possible a relatively easy β-fragmentation, which provides ^{3}**IV** by homolytic N−S bond cleavage. After intensive mechanistic studies on the possible pathway, we concentred our attention on a chain reaction[84,85]. Enallene activation, cyclization and fragmentation represent the initiation of the process. The propagation involves the addition of sulfonyl radical to the diagonal carbon of the allene, affording radical intermediate ^{2}**V**. Starting from this point, two possible pathways are energetically possible. β-fragmentation of ^{2}**V**, through a barrier of +21.4 kcal/mol in ΔG, regenerate sulfonyl radical and afford α,β-unsaturated imine VI. A further activation via eT provide ^{3}**VI** by analogy to the activation of **5** and **7** that is nearly isoenergetic. Conversion of ^{3}**VI** in ^{3}**VII** easily takes place through 5-*exo-trig* cyclization and ISC closed the sequence affording product **8**.

In an alternative scenario, 7-*endo-trig* cyclization of allyl radical ^{2}**V**, which occurs through a barrier of +17.6 kcal/mol in ΔG, led to radical ^{2}**VIII**. The following 4-*exo-trig*/5-*endo-trig* cyclization is the most energetically expensive step of the pathway (barrier of +24.9 kcal/mol in ΔG), and it affords [3.2.0] bicyclic radical unit ^{2}**IX**. β-fragmentation delivers product **8** and regenerates a sulfonyl radical that propagates the process. Overall, the propagation of this chain reaction has a largely negative ΔG (−23.6 kcal/mol) (Scheme 37). All steps of the sequence are exergonic and the energy of the system progressively decrees, making the propagation easier. Starting from ^{2}**V**, the energy difference between the TS that led to **VI** and the higher TS in the alternative chain propagation is only 0.5 Kcal/mol, too little to define a preferential route. It exists, on the contrary, a major difference between the chain generating **VI** (−7.3 kcal/mol) and the chain that afford **4** directly (−23.6 kcal/mol). This gap, joined to an additional eT necessary to convert **VI** into the product **4**, suggests that the process follows a free-radical pathway. Despite β-fragmentation of the C-S bond, which is a common method used in organic synthesis, N-S bond cleavage triggered by a sulfonamidoyl radical had few precedents in literature[86–88] and, in no case reincorporation of the sulfonyl radical is observed.



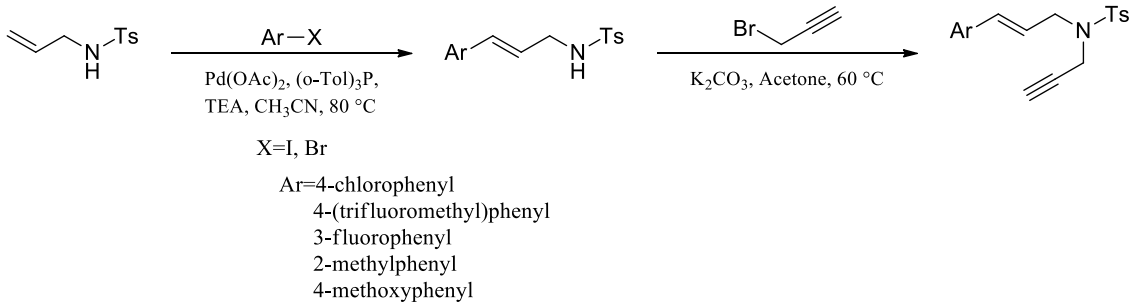
Scheme 37 proposed reaction mechanism for 1,6 enallenamides.

3.3 Conclusion

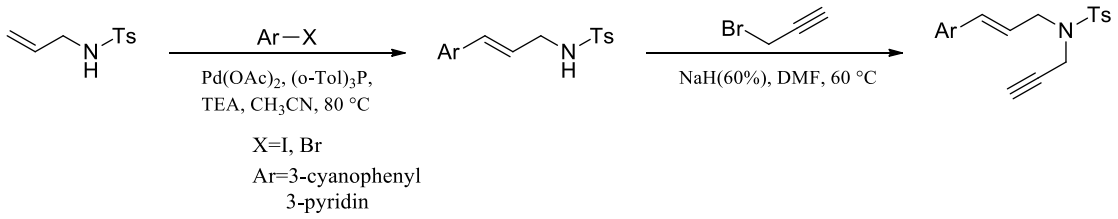
In conclusion, we developed a procedure for the preparation of two families of 3.2.0 bicyclic structures from enallenes. The method shows excellent regio- and stereoselectivity, affording complex architectures under mild conditions. Mechanistic studies reveal two orthogonal pathways trigger by the same reaction condition, a 2+2 photocycloaddition and a radical chain indirectly initiated via eT by a photoexcited iridium complex. The fragmentation/recombination sequence herein reported is unprecedent in sequences promoted by visible light.

3.4 Experimental section

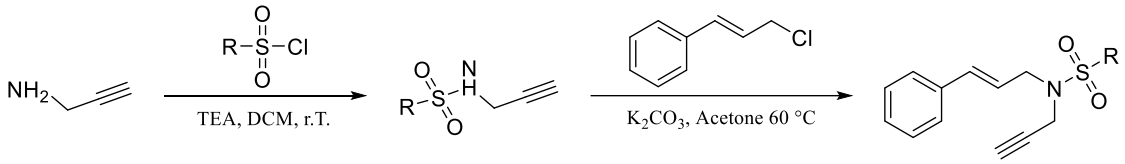
Synthesis of 1,6 enynes



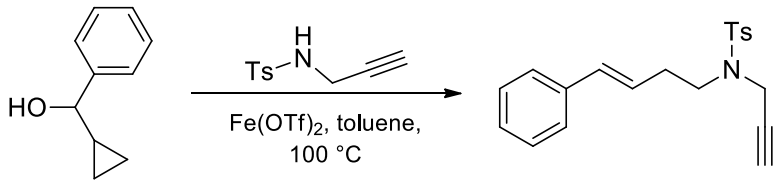
N-allyl-4-methylbenzenesulfonamide (1 equiv.), $(o\text{-Tol})_3P$ (0.1 equiv.) and $Pd(OAc)_2$ (0.05 equiv.) were sequentially added to a Schlenk tube equipped with magnetic stirring bar. CH_3CN (0.41 M), TEA (2 equiv.) and the desired aryl halide (1 equiv.) were added under N_2 atmosphere and the mixture was stirred at 80 °C for 3 hours. A second batch of the desired aryl halide (0.42 equiv.), $Pd(OAc)_2$ (0.026 equiv.) and $(o\text{-Tol})_3P$ (0.05 equiv.) were then added. The mixture was stirred at 80 °C for further 6 hours, allowed to cool to room temperature, diluted with water and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentred under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 9:1). The substituted cinnamyl tosylamide (1 equiv.) was dissolved in acetone (0.2 M). K_2CO_3 (3 equiv.) and propargyl bromide (85% in toluene, 1.5 equiv.) were then added. The mixture was subsequently placed in a preheated oil bath at 60 °C and stirred overnight. After consumption of the starting material, the reaction mixture was cooled down to room temperature and water was added. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic fractions were dried over Na_2SO_4 10 and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 8:2).



The Heck-type coupling was performed according to the above-mentioned procedure. Then, the resulting tosylamide (1 equiv.) was dissolved in DMF (0.2 M). NaH (60% in mineral oil, 1.3 equiv.) was added slowly at 0° C under vigorous stirring. The resulting mixture was stirred for 1 hour at room temperature prior to the addition of a propargyl bromide solution (85% in toluene, 1.5 equiv.). The resulting mixture was then heated at 60° C for 2 hours. After completion, the reaction mixture was cooled down to room temperature and water was added. The mixture was extracted with EtOAc (3 x 30 mL) and the organic layers washed with a sat. LiCl solution. The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by chromatography on silica gel (nhexane/EtOAc 8:2).



DCM (0.4 M), TEA (1.1 eq) and propargyl amine (1 equiv.) were added to a 100 mL round bottom flask equipped with magnetic stirring bar. The resulting mixture was stirred at 0 °C and sulfonyl halide (1.05 eq) was added slowly. The reaction mixture was stirred at room temperature for 12 hours, quenched with sat NH_4Cl, diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentred under reduced pressure. Whitout isolation, propargyl tosylamide was transferred in a Schlenk tube equipped with a magnetic stirring bar and K_2CO_3 (1.5 equiv.). Acetone (0.33 M) and cinnamyl chloride (1.3 equiv.) were then added. The reaction mixture was stirred at 60 °C overnight. The mixture was cooled to room temperature, diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentred under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 9:1).



$Fe(OTf)_2$ (0.1 equiv.) and toluene (0.17 M) were added to a Schlenk tube equipped with magnetic stirring bar. The resulting mixture was stirred at room temperature for 10 minutes prior to the addition of a solution of cyclopropyl(phenyl)methanol (1 equiv.) and 4-methyl-N- (prop-2-yn-1-yl)benzenesulfonamide (4 equiv.) in toluene (0.17 M). The mixture was stirred at 100 °C and conversion was monitoring by TLC. The reaction mixture was then cooled and the solvent removed under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 9:1).

General procedure 1a (GP-1a)

CuI (0.1 equiv.), paraformaldehyde (1.6 equiv.), the desired 1,6-enyne (1 equiv.) and dioxane (1.5 M) were sequentially added to a 50 mL two-necked round-bottom flask equipped with a magnetic stirring. The resulting mixture was stirred at room temperature for 10 minutes prior to the addition of iPr_2NH (1.4 equiv.). The mixture was then heated to 110 °C for 12 hours 11 under air and then cooled down to room temperature. A sat. NH_4Cl solution was added. The mixture was diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentred under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 95:5).

General procedure 1b (GP-1b)

ZnI_2 (0.8 equiv.), the desired aldehyde (1.8 equiv.), 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (1 equiv.) and toluene (0.33 M) were sequentially added to a 50 mL two-necked round-bottom flask equipped with a magnetic stirring bar. The resulting mixture was stirred at room temperature for 10 minutes prior to the addition of morpholine (1.4 equiv.). The mixture was then heated to 110 °C for 12 hours under air and then cooled down to room temperature. A saturated NH_4Cl solution was added. The mixture was diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentred under reduced pressure. The

resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 8:2). The intermediate was dissolved in acetone (0.33 M). K_2CO_3 (1.5 equiv.) and cinnamylchloride (1.3 equiv.) were sequentially added. The mixture was stirred at 60 °C monitoring the conversion by TLC. Upon full conversion, the mixture was diluted with EtOAc (20 mL) and washed with water. The combined organic layers were dried over Na_2SO_4, filtered and concentred under reduced pressure. The resulting crude was purified by chromatography on silica gel (n-hexane/EtOAc 95:5).

General procedure 2 (GP-2)

The desired alkyne (1 equiv.) and THF (0.17 M) were sequentially added to a Schlenk tube equipped with a magnetic stirring bar. the resulting mixture was stirred at room temperature for 10 minutes prior to the addition of tBuOK (0.3 equiv.). After complete conversion as monitored by TLC, a saturated NH_4Cl solution (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 solution was concentrated under reduced pressure and the crude purified by chromatography on silica gel (n-hexane/EtOAc 95:5).

General procedure 3 (GP-3)

To a vial charged with substrate (1eq.) and PC4 (0.01 eq), dry and degassed DMF (0.05 M) were added. The solution was transferred in two NMR tubes and degassed with three freeze-pump cycles. The homogeneous solution was placed in an oil bath at room temperature and irradiated with LED stripes for 6 hours. The mixture was then concentrated and the residue purified by chromatography on silica gel.

N-(buta-2,3-dien-1-yl)-N-cinnamyl-4-methylbenzenesulfonamide 5a was isolated following the **GP-1a**. Yield **29%** (182.7 mg, 0.54 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.50 – 6.73 (m, 7H), 6.43 (d, *J* = 15.8 Hz, 1H), 5.96 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.91 (p, *J* = 6.9 Hz, 1H), 4.67 (dt, *J* = 6.6, 2.5 Hz, 2H), 3.98 (d, *J* = 6.8, Hz, 2H), 3.87 (dt, *J* = 7.2, 2.5 Hz, 2H), 2.40 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 209.6 (Cq), 143.4 (Cq), 137.5 (Cq), 136.3 (Cq), 134.2 (CH), 129.8 (CH), 128.6 (CH), 127.9 (CH), 127.3 (CH), 126.5 (CH), 123.7 (CH), 85.8 (CH), 76.3 (CH_2), 48.9 (CH_2), 45.8 (CH_2), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{22}NO_2S$ $[M+H]^+$ 340.14 found 340.20

(E)-N-(buta-2,3-dien-1-yl)-N-(3-(4-chlorophenyl)allyl)-4-methylbenzenesulfonamide 5b was isolated following the **GP-1a**. Yield **61%** (197.0 mg, 0.53 mmol). White solid. **^{1}H NMR (300 MHz, Acetone) δ =** 7.83 – 7.73 (m, 2H), 7.48 – 7.27 (m, 6H), 6.56 (dt, *J* = 15.8, 1.5 Hz, 1H), 6.10 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.99 (p, *J* = 6.9 Hz, 1H), 4.75 (dt, *J* = 6.6, 2.5 Hz, 2H), 4.02 (d, *J* = 6.6 Hz, 2H), 3.90 (dt, *J* = 7.1, 2.6 Hz, 2H), 2.42 (s, 3H). **^{13}C NMR (75 MHz, Acetone)** δ = 209.5 (Cq), 143.4 (Cq), 137.8 (Cq), 135.5 (Cq), 132.9 (Cq), 132.4 (CH), 129.8 (CH), 128.6 (CH), 128.0 (CH), 127.3 (CH), 125.1 (CH), 85.6 (CH), 75.6 (CH_2), 48.7 (CH_2), 45.9 (CH_2), 20.6 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{20}ClNNaO_2S$ $[M+Na]^+$ 396.08 found 396.30

(E)-N-(buta-2,3-dien-1-yl)-4-methyl-N-(3-(4-(trifluoromethyl)phenyl)allyl)benzenesulfonamide 5c was isolated following the **GP-1a**. Yield **66%** (212.0 mg, 0.52 mmol). White solid. **^{1}H NMR (400 MHz, $CDCl_3$) δ =** 7.76 – 7.70 (m, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.12 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.96 (p, *J* = 6.8 Hz, 1H), 4.69 (dt, *J* = 6.5, 2.5 Hz, 2H), 4.02 (d, *J* = 6.6 Hz, 2H), 3.89 (dt, *J* = 7.1, 2.5 Hz, 2H), 2.42 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 209.7 (Cq), 143.5 (Cq), 139.8 (Cq), 137.3 (Cq), 132.4 (CH), 129.8 (CH), 129.6 (q, J = 32.1 Hz, Cq), 127.2 (CH), 126.8 (CH), 126.6 (CH), 125.5 (q, *J* = 4.1 Hz), 124,1 (q, *J* = 271.5 Hz, Cq), 85.7 (CH), 76.3 (CH_2), 48.7 (CH_2), 46.2 (CH_2), 21.5 (CH_3). **^{19}F NMR (564 MHz, $CDCl_3$) δ =** -62.44. **(ESI)-MS** calcd for $C_{21}H_{20}F_3NNaO_2S$ $[M+Na]^+$ 430.11 found 430.01.

(E)-N-(buta-2,3-dien-1-yl)-N-(3-(3-fluorophenyl)allyl)-4-methylbenzenesulfonamide 5d was isolated following the **GP-1a**. Yield **41%** (102.2 mg, 0.29 mmol). White solid. **^{1}H NMR (400 MHz, $CDCl_3$) δ =** 7.75 (d, *J* = 8.2 Hz, 2H), 7.37 – 7.23 (m, 3H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.00 – 6.90 (m, 2H), 6.44 (d, *J* = 15.8 Hz, 1H), 6.01 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.97 (p, *J* = 6.8 Hz, 1H), 4.72 (dt, *J* = 6.5, 2.5 Hz, 1H), 4.72 (dt, *J* = 6.5, 2.5 Hz, 2H), 4.03 (d, *J* = 6.7 Hz, 1H), 3.94 – 3.88 (m, 2H), 2.45 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 209.8 (Cq), 163.0 (d, *J* = 245.4 Hz, Cq), 143.4 (Cq), 138.6 (d, *J* = 7.9 Hz, Cq), 137.5 (Cq), 132.8 (d, *J* = 2.3 Hz, CH), 130.0 (d, *J* = 8.5 Hz, CH), 129.8 (CH), 127.24 (CH), 125.3 (CH), 122.3 (d, *J* = 2.9 Hz, CH), 114.7 (d, *J* = 21.3 Hz, CH), 112.9 (d, *J* = 22.0 Hz, CH), 85.8 (CH), 76.2 (CH_2), 48.7 (CH_2), 46.0 (CH_2), 21.5 (CH_3). **^{19}F NMR (564 MHz, $CDCl_3$)** δ = -113.24. **(ESI)-MS** calcd for $C_{20}H_{20}FNNaO_2S$ $[M+Na]^+$ 380.11 found 379.94.

(E)-N-(buta-2,3-dien-1-yl)-N-(3-(3-cyanophenyl)allyl)-4-methylbenzenesulfonamide 5e was isolated following the **GP-1a**. Yield **39%** (100.1 mg, 0.27 mmol). White solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.72 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 3H), 7.45 – 7.36 (m, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.13 – 6.01 (m, 1H), 4.94 (p, *J* = 6.8 Hz, 1H), 4.74 – 4.66 (m, 2H), 4.01 (d, *J* = 6.5 Hz, 2H), 3.88 (dd, *J* = 6.6, 3.1 Hz, 2H), 2.43 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 209.7 (Cq), 143.6 (Cq), 137.6 (Cq), 137.4 (Cq), 131.5 (CH), 131.1 (CH), 130.5 (CH), 129.9 (CH), 129.8 (CH), 129.4 (CH), 127.2 (CH), 127.1 (CH), 118.6 (Cq), 112.9 (Cq), 87.2 (CH), 76.3 (CH_2), 48.6 (CH_2), 46.3 (CH_2), 21.5 (CH_3). **(ESI)-MS** calcd for $C_{21}H_{20}N_2NaO_2S$ $[M+Na]^+$ 387.11 found 387.19. **(ESI)-MS** calcd for $C_{21}H_{20}N_2NaO_2S$ $[M+Na]^+$ 387.11 found 387.01.

(E)-N-(buta-2,3-dien-1-yl)-4-methyl-N-(3-(m-tolyl)allyl)benzenesulfonamide 5f was isolated following the **GP-1a**. Yield **63%** (41.5 mg, 0.12 mmol). White solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.74 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.24 (m, 3H), 7.21 – 7.09 (m, 3H), 6.68 (d, *J* = 15.7 Hz, 1H), 5.86 (dt, *J* = 15.7, 6.8 Hz, 1H), 5.01 – 4.90 (m, 1H), 4.71 (dt, *J* = 6.7, 2.5 Hz, 2H), 4.03 (d, *J* = 6.9 Hz, 2H), 3.91 (dt, *J* = 7.2, 2.5 Hz, 2H), 2.43 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 207.8 (Cq), 143.4 (Cq), 137.6 (Cq), 135.4 (Cq), 135.4 (CH) 132.2 (CH), 130.3 (Cq), 129.8 (CH), 127.8 (CH), 127.2 (CH), 126.1 (CH), 125.8 (CH), 125.0 (CH), 85.8 (CH), 75.4 (CH_2), 49.0 (CH_2), 45.6 (CH_2),

21.5 (CH_3), 19.8 (CH_3). **(ESI)-MS** calcd for $C_{21}H_{23}NNaO_2S$ $[M+Na]^+$ 376.16 found 376.05.

(E)-N-(buta-2,3-dien-1-yl)-N-(3-(4-methoxyphenyl)allyl)-4-methylbenzenesulfonamide 5g was isolated following the **GP-1a**. Yield **73%** (127.5 mg, 0.34 mmol). White solid **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.73 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 7.25 – 7.17 (m, 2H), 6.89 – 6.78 (m, 2H), 6.40 (d, *J* = 15.8 Hz, 1H), 5.84 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.93 (p, *J* = 6.9 Hz, 1H), 4.69 (dt, *J* = 6.6, 2.5 Hz, 2H), 3.98 (d, *J* = 6.8 Hz, 1H), 3.89 (dt, *J* = 7.1, 2.5 Hz, 2H), 3.80 (s, 3H), 2.42 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 209.6 (Cq), 159.4 (Cq), 143.3 (Cq), 137.6 (Cq), 133.7 (CH), 129.7 (CH), 129.0 (Cq), 127.7 (CH), 127.2 (CH), 121.3 (CH), 114.0 (CH), 85.8 (CH_2), 76.2 (CH), 55.3 (CH_3), 49.0 (CH_2), 45.6 (CH_2), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{21}H_{23}KNO_3S$ $[M+K]^+$ 408.10 found 408.14.

(E)-N-(buta-2,3-dien-1-yl)-4-methyl-N-(3-(pyridin-3-yl)allyl)benzenesulfonamide 5h was isolated following the **GP-1a**. Yield **67%** (140.3 mg, 0.41 mmol). White solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 8.02 – 7.54 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.54 (d, *J* = 15.5 Hz, 1H), 6.14 – 6.03 (m, 1H), 4.93 (p, *J* = 6.9 Hz, 1H), 4.69 (dt, *J* = 6.6, 2.4 Hz, 2H), 4.03 (d, *J* = 6.1 Hz, 2H), 3.89 (dt, *J* = 7.2, 2.4 Hz, 2H), 2.42 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ = 209.6 (Cq), 143.5 (Cq), 137.3 (Cq), 129.8 (CH), 127.2 (CH), 126.9 (CH), 85.7 (CH), 76.4 (CH_2), 48.8 (CH_2), 46.1 (CH_2), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{19}H_{21}N_2O_2S$ $[M+H]^+$ 341.13 found 340.90

(E)-(3-(buta-2,3-dien-1-yloxy)prop-1-en-1-yl)benzene (5j), Analytical data correspond to literature[28]

To a 50 mL two-neck round-bottom flask equipped with a magnetic stirring bar were added CuBr (103.8 mg, 0.72 mmol), paraformaldehyde (109 mg, 3.62 mmol), the corresponding enyne (250 mg, 1.45 mmol) and dioxane (5.3 mL). The resulting mixture was stirred at room temperature before addition of *i*Pr_2NH (410 μL, 2.90 mmol). The mixture was stirred at 110 °C without protection with an inert atmosphere. After 12 h, the reaction mixture was cooled to room temperature and sat NH_4Cl was added. The mixture was diluted with water and extracted with dietyl ether (3x10 mL). The combined organic

layer was dried over Na_2SO_4, filtered and concentred under reduced pressure. The resulting crude was purified by chromatography on silica gel (*n*-hexanes/EtOAc 97:3) afforded 1j (120.1 mg, 44%) as a yellow liquid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.50 – 7.20 (m, 5H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.1 Hz, 1H), 5.33 (p, *J* = 6.8 Hz, 1H), 4.86 (dt, *J* = 6.6, 2.4 Hz, 2H), 4.22 (dd, *J* = 6.1, 1.5 Hz, 2H), 4.12 (dt, *J* = 7.0, 2.5 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 209.4 (Cq), 136.7 (Cq), 132.7 (CH), 128.6 (CH), 127.7 (CH), 126.5 (CH), 125.8 (CH), 87.8 (CH), 75.8 (CH_2), 70.5 (CH_2), 67.9 (CH_2).

N-cinnamyl-N-(3-cyclohexylideneallyl)-4-methylbenzenesulfonamide (5k). In a schlenk tube under nitrogen atmosphere CuBr (28.6 mg, 0.2 mmol), toluene (2 mL), 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (420 mg, 2.0 mmol) and cyclohexanone (239 mg, 2.2 mmol) were added in this order. The resulting mixture was stirred at room temperature before addition of pyrrolidine (182 µL, 2.2 mmol) and then heated at 100° C. After 3 h the reaction mixture was cooled and filtered through a short pad of silica gel eluented with acetone (70 mL). The above crude product was then dissolved in toluene (6 mL), transferred to the Schlenk tube containing ZnI_2 (191.4 mg, 1.2 mmol). The Schlenk tube was placed in a pre-heated oil bath at 120° C with stirring. After 7 h, the reaction was complete as monitored by TLC, the crude reaction mixture was filtrated through a short pad of silica gel eluented with acetone (50 mL). The resulting crude was purified by chromatography on silica gel (*n*-hexanes/EtOAc 9:1) afforded N-(3-cyclohexylideneallyl)-4-methylbenzenesulfonamide (148.0mg, 25 %) as a white solid1. N-(3-cyclohexylideneallyl)-4-methylbenzenesulfonamide was transferred in a Schlenk tube equipped with a magnetic stirring bar and K_2CO_3 (105 mg, 0.76 mmol), Acetone (1.5 mL) and cinnamyl chloride (103 µL, 0.66 mmol) were added. The reaction mixture was stirred at 60 °C. After 18 h the mixture was cooled to r.T. diluted with water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentred under reduced pressure. The resulting crude was purified by chromatography on silica gel (*n*-hexanes/EtOAc 9:1) afforded 1k (152 mg, 70%) as a white solid.**^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.74 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.20 (m, 7H), 6.44 (d, *J* = 15.8 Hz, 1H), 5.98 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.75 (tt, *J* = 6.8, 2.0 Hz, 1H), 4.03 (dd, *J* = 6.5, 1.3 Hz, 2H), 3.84 (d, *J* = 6.9 Hz, 2H), 2.42 (s, 3H), 2.15 – 1.99 (m, 4H), 1.60 – 1.46 (m,

6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 200.2 (Cq), 143.2 (Cq), 137.8 (Cq), 136.3 (Cq), 133.9 (CH), 129.7 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 126.4 (CH), 123.9 (CH), 103.9 (Cq), 84.0 (CH), 48.3 (CH_2), 46.8 (CH_2), 31.3 (CH_2), 27.2 (CH_2), 25.9 (CH_2), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{25}H_{29}NNaO_2S$ $[M+Na]^+$ 430.18 found 430.03.

N-cinnamyl-N-(hexa-2,3-dien-1-yl)-4-methylbenzenesulfonamide 5i was isolated following the **GP-1b**. Yield **5%** (36.7 mg, 0.1 mmol). Viscous oil. **^{1}H NMR (400 MHz, Acetone)** δ = 7.80 (d, *J* = 8.3 Hz, 2H), 7.44 (dd, *J* = 8.6, 0.8 Hz, 2H), 7.45 – 7.22 (m, 5H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.08 (dt, *J* = 15.9, 6.6 Hz, 1H), 5.31 – 5.21 (m, 1H), 5.05 – 4.94 (m, 1H), 4.05 (d, *J* = 6.9 Hz, 2H), 3.89 (dd, *J* = 6.9, 2.3 Hz, 2H), 2.45 (s, 3H), 2.04 – 1.92 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz, Acetone)** δ = 205.6 (Cq), 144.2 (Cq), 138.9 (Cq), 137.4 (Cq), 134.5 (CH), 130.6 (CH), 129.4 (CH), 128.6 (CH), 128.1 (CH), 127.3 (CH), 124.9 (CH), 94.8 (CH), 87.9 (CH_2), 49.5 (CH_2), 47.3 (CH_2), 22.3 (CH_2), 21.4 (CH_3), 13.8 (CH_3). **(ESI)-MS** calcd for $C_{22}H_{25}NNaO_2S$ $[M+Na]^+$ 390.15 found 390.23.

N-cinnamyl-4-methyl-N-(4-phenylbuta-2,3-dien-1-yl)benzenesulfonamide 5l was isolated following the **GP-1b**. Yield **22%** (91.0 mg, 0.22 mmol). White solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.78 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.07 (m, 12H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.15 (dt, *J* = 6.4, 2.3 Hz, 1H), 5.99 (dt, *J* = 15.8, 6.8 Hz, 1H), 5.42 (q, *J* = 6.7 Hz, 1H), 4.20 – 3.92 (m, 4H), 2.45 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 206.4 (Cq), 143.4 (Cq), 137.5 (Cq), 136.1 (Cq), 134.3 (CH), 133.5 (Cq), 129.8 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 127.3 (CH), 126.9 (CH), 126.4 (CH), 123.4 (CH), 96.0 (CH), 90.6 (CH), 49.0 (CH_2), 45.8 (CH_2), 21.5 (CH_3). **(ESI)-MS** calcd for $C_{26}H_{25}KNO_2S$ $[M+K]^+$ 454.12 found 453.98

N-cinnamyl-4-methyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide 7a was isolated following the **GP-2**. Yield **67%** (560.0 mg, 1.72 mmol). White solid. **^{1}H NMR (400 MHz, $CDCl_3$) δ =** 7.72 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.20 (m, 7H), 6.89 (t, *J* = 6.2 Hz, 1H), 6.45 (d, *J* = 15.9 Hz, 1H), 5.98 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.31 (d, *J* = 6.2 Hz, 2H), 3.98 (dd, *J* = 6.2, 1.4 Hz, 2H), 2.40 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ = ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9 (Cq), 143.8 (Cq), 136.5 (Cq), 135.7 (Cq), 133.6 (CH), 129.8 (CH),

128.5 (CH), 127.8 (CH), 127.3 (CH), 126.4 (CH), 123.5 (CH), 100.1 (CH), 88.0 (CH_2), 48.6 (CH_2), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{19}H_{19}NNaO_2S$ $[M+Na]^+$ 348.10 found 347.97.

(E)-4-methyl-N-(propa-1,2-dien-1-yl)-N-(3-(o-tolyl)allyl)benzenesulfonamide 7b was isolated following the **GP-2**. Yield **56%** (78.7 mg, 0.23 mmol).Viscous clear oil. **^{1}H NMR** (400 MHz, Acetone) δ = 7.80 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.35 – 7.27 (m, 1H), 7.18 – 7.09 (m, 2H), 6.92 (t, *J* = 6.3 Hz, 1H), 6.78 (d, *J* = 15.8 Hz, 1H), 5.92 (dt, *J* = 15.8, 6.1 Hz, 1H), 5.41 (d, *J* = 6.3 Hz, 2H), 4.05 (dd, *J* = 6.1, 1.5 Hz, 2H), 2.44 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, Acetone) δ 201.9 (Cq), 144.0 (Cq), 136.1 (Cq), 135.6 (Cq), 135.2 (Cq), 131.1 (CH), 130.1 (CH), 129.8 (CH), 127.5 (CH), 127.3 (CH), 126.02 (CH), 125.6 (CH), 125.0 (CH), 99.8 (CH), 87.3 (CH_2), 48.6 (CH_2), 20.5 (CH_3), 18.8 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{22}NO_2S$ $[M+H]^+$ 340.14 found 340.10.

(E)-N-(3-(4-methoxyphenyl)allyl)-4-methyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide 7c was isolated following the **GP-2**. Yield **49%** (38.6 mg, 0.11 mmol). Pale viscous oil. **^{1}H NMR (400 MHz, Acetone)** δ = 7.78 (d, *J* = 8.3 Hz, 2H), 7.49 – 7.40 (m, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.95 – 6.83 (m, 3H), 6.47 (d, *J* = 15.9 Hz, 1H), 5.91 (dt, *J* = 15.9, 6.3 Hz, 1H), 5.38 (d, *J* = 6.3 Hz, 2H), 3.98 (d, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 2.43 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 207.1 (Cq), 164.8 (Cq), 149.2 (Cq), 141.2 (Cq), 138.3 (CH), 135.0 (CH), 134.4 (Cq), 132.8 (CH), 132.5 (CH), 126.2 (CH), 119.1 (CH), 104.9 (CH), 92.6 (CH_2), 59.9 (CH_2), 53.7 (CH_3), 25.8 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{21}KNO_3S$ $[M+K]^+$ 394.09 found 394.14.

(E)-N-(3-(4-chlorophenyl)allyl)-4-methyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide 7d was isolated following the **GP-2**. Yield **37%** (111.2 mg, 0.31 mmol). White solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.02 (m, 4H), 6.88 (t, *J* = 6.2 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.95 (dt, *J* = 15.9, 6.1 Hz, 1H), 5.30 (d, *J* = 6.2 Hz, 2H), 3.95 (d, *J* = 6.5 Hz,1H), 2.41 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 201.8 (Cq), 143.8 (Cq), 135.7 (Cq), 135.0 (Cq), 133.4 (Cq), 132.1 (CH), 129.7 (CH), 128.6 (CH), 127.5 (CH), 127.3 (CH), 124.2 (CH), 100.1 (CH), 87.9

(CH_2), 48.4 (CH_2), 21.5 (CH_3). **(ESI)-MS** calcd for $C_{19}H_{19}ClNO_2S$ $[M+H]^+$ 360.08 found 360.14.

(E)-N-(3-(3-cyanophenyl)allyl)-4-methyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide 7e was isolated following the **GP-2**. Yield **27%** (54.3 mg, 0.15 mmol). Viscous yellow oil. **^{1}H NMR (400 MHz, Acetone) δ =** 7.79 (d, *J* = 8.0 Hz, 2H), 7.73 – 7.61 (m, 3H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 6.93 (t, *J* = 6.3 Hz, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.23 (dt, *J* = 16.1, 6.0 Hz, 1H), 5.40 (d, *J* = 6.2 Hz, 2H), 4.06 (d, *J* = 5.7 Hz, 2H), 2.42 (s, 1H). **^{13}C NMR (101 MHz, Acetone)** δ = 201.8 (Cq), 144.1 (Cq), 138.0 (Cq), 136.0 (Cq), 131.0 (CH), 130.9 (CH), 130.6 (CH), 129.8 (CH), 129.7 (CH), 129.7 (CH), 127.3 (CH), 126.7 (CH), 118.3 (Cq), 112.7 (Cq), 99.8 (CH), 87.6 (CH_2), 48.1 (CH_2), 20.6 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{18}N_2NaO_2S$ $[M+Na]^+$ 373.10 found 373.18.

N-cinnamyl-N-(propa-1,2-dien-1-yl)methanesulfonamide 7f was isolated following the **GP-2**. Yield **50%** (124.5 mg, 0.50 mmol) .White solid. **^{1}H NMR (400 MHz, $CDCl_3$) δ =** 7.40 – 7.22 (m, 5H), 6.73 (tt, *J* = 6.2, 0.7 Hz, 1H), 6.73 (tt, *J* = 6.2, 0.7 Hz, 1H), 6.18 (dt, *J* = 15.9, 6.5 Hz, 1H), 5.44 (d, *J* = 6.3 Hz, 2H), 4.15 (ddd, *J* = 6.4, 1.4, 0.7 Hz, 2H), 4.17 – 4.12 (m, 2H), 2.93 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 201.3 (Cq), 136.2 (Cq), 134.3 (CH), 128.7 (CH), 128.1 (CH), 126.5 (CH), 123.0 (CH), 99.7 (CH), 88.2 (CH_2), 48.1 (CH_2), 39.1 (CH_3). **(ESI)-MS** calcd for $C_{13}H_{16}NO_2S$ $[M+H]^+$ 250.09 found 250.22.

(E)-N-(propa-1,2-dien-1-yl)-N-(3-(o-tolyl)allyl)methanesulfonamide 7g was isolated following the **GP-2**. Yield **25%** (43.7 mg, 0.17 mmol). Pale yellow solid. **^{1}H NMR (400 MHz, Acetone)** δ 7.51 – 7.43 (m, 1H), 7.20 – 7.11 (m, 3H), 6.88 (dd, *J* = 15.8, 1.6 Hz, 1H), 6.76 (t, *J* = 6.3 Hz, 1H), 6.13 (dt, *J* = 15.7, 6.2 Hz, 1H), 5.49 (d, *J* = 6.3 Hz, 2H), 4.18 (d, *J* = 6.2 Hz, 2H), 3.04 (s, 3H), 2.33 (s, 3H). **^{13}C NMR (101 MHz, Acetone)** δ = 201.4 (Cq), 135.6 (Cq), 135.3 (Cq), 131.4 (CH), 130.2 (CH), 127.6 (CH), 126.1 (CH), 125.6 (CH), 125.3 (CH), 99.6 (CH), 87.4 (CH_2), 48.5 (CH_2), 38.0 (CH_3), 18.9 (CH_3). **(ESI)-MS** calcd for $C_{14}H_{18}NO_2S$ $[M+H]^+$ 264.11 found 264.40.

N-cinnamyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide 7h was isolated following the **GP-2**. Yield **68%** (252.2 mg, 0.81 mmol). Pale white solid. **^{1}H NMR (400 MHz, Acetone)** δ = 7.93 (d, *J* = 7.6 Hz, 2H), 7.82 – 7.56 (m, 3H), 7.40 – 7.22 (m, 5H), 6.91 (t, *J* = 6.3 Hz, 1H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.09 (dt, *J* = 15.9, 6.1 Hz, 1H), 5.39 (d, *J* = 6.2 Hz, 2H), 4.04 (d, *J* = 6.1 Hz, 2H). **^{13}C NMR (101 MHz, Acetone)** δ = 201.9 (Cq), 138.8 (Cq), 136.6 (Cq), 133.4 (CH), 133.1 (CH), 129.3 (CH), 128.5 (CH), 127.7 (CH), 127.2 (CH), 126.3 (CH), 123.6 (CH), 99.7 (CH), 87.4 (CH_2), 48.5 (CH_2). **(ESI)-MS** calcd for $C_{18}H_{18}NO_2S$ $[M+H]^+$ 312.11 found 312.17.

N-cinnamyl-2,4,6-trimethyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide 7j was isolated following the **GP-2**. Yield **40%** (108.2 mg, 0.31 mmol). Viscous liquid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.34 – 7.16 (m, 4H), 6.94 (s, 2H), 6.89 (t, *J* = 6.3 Hz, 1H), 6.30 (d, *J* = 15.9 Hz, 1H), 5.94 (dt, *J* = 15.9, 6.4 Hz, 1H), 5.36 (d, *J* = 6.3 Hz, 2H), 3.96 (d, *J* = 6.3 Hz, 1H), 2.64 (s, 6H), 2.26 (s, 3H).**^{13}C NMR (75 MHz, Acetone)** δ = 200.7 (Cq), 143.2 (Cq), 139.9 (CH), 136.6 (Cq), 133.4 (CH), 133.2 (Cq), 132.1 (CH), 128.5 (CH), 127.6 (CH), 126.2 (CH), 123.2 (CH), 99.5 (CH), 87.7 (CH_2), 47.4 (CH_2), 22.3 (CH_3), 20.0 (CH_3). **(ESI)-MS** calcd for $C_{21}H_{24}NO_2S$ $[M+H]^+$ 354.14 found 354.04.

N-cinnamyl-4-nitro-N-(propa-1,2-dien-1-yl)benzenesulfonamide 7k was isolated following the **GP-2**. Yield **25%** (89.6 mg, 0.25 mmol). Viscous yellow oil. **^{1}H NMR (300 MHz, Acetone)** δ = 8.33 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.40 – 7.22 (m, 5H), 6.88 (t, *J* = 6.2 Hz, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 5.95 (dt, *J* = 15.8, 6.3 Hz, 1H), 5.40 (d, *J* = 6.2 Hz, 2H), 4.07 (d, *J* = 6.4 Hz, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 201.8 (Cq), 150.1 (Cq), 144.4 (Cq), 135.9 (Cq), 134.5 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 126.3 (CH), 124.3 (CH), 122.3 (CH), 99.4 (CH) ,88.5 (CH_2), 49.1 (CH_2). **(ESI)-MS** calcd for $C_{18}H_{17}N_2O_4S$ $[M+H]^+$ 357.09 found 357.19.

4-chloro-N-cinnamyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide 7i was isolated following the **GP-2**. Yield **67%** (168.2 mg, 0.49 mmol). White solid. **^{1}H NMR (300 MHz, Acetone) δ =** 7.91 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.48 – 7.18 (m, 5H), 6.89 (t, *J* = 6.3 Hz, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.07 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.41 (d, *J* = 6.3 Hz, 2H), 4.04 (d, *J* = 6.2 Hz, 2H).**^{13}C NMR (75 MHz, Acetone)** δ = 202.0

(Cq), 138.9 (Cq), 137.5 (Cq), 136.5 (Cq), 133.6 (CH), 129.5 (CH), 129.1 (CH), 128.5 (CH), 127.8 (CH), 126.3 (CH), 123.2 (CH), 99.4 (CH_2), 87.6 (CH), 48.6 (CH_2). **(ESI)-MS** calcd for $C_{18}H_{17}ClNO_2S$ $[M+H]^+$ 346.07 found 346.11.

N-cinnamyl-N-(propa-1,2-dien-1-yl)naphthalene-1-sulfonamide 7l was isolated following the **GP-2**. Yield **78%** (105.9 mg, 0.29 mmol). Viscous liquid. **^{1}H NMR (300 MHz, Acetone)** δ = 8.57 – 8.51 (m, 1H), 8.17 – 8.08 (m, 2H), 8.07 – 8.00 (m, 1H), 7.90 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.77 – 7.72 (m, 2H), 7.33 – 7.14 (m, 5H), 6.98 (t, *J* = 6.3 Hz, 1H), 6.54 (dt, *J* = 15.8, 1.5 Hz, 1H), 6.07 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.36 (d, *J* = 6.3 Hz, 2H), 4.08 (d, *J* = 6.2 Hz, 2H), 2.84 (s, 3H). **^{13}C NMR (75 MHz, Acetone)** δ = 201.9 (Cq), 136.6 (Cq), 135.9 (Cq), 135.0 (Cq), 133.4 (CH), 132.3 (Cq), 129.5 (CH), 129.4 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 126.3 (CH), 123.5 (CH), 122.5 (CH), 99.7 (CH_2), 87.5 (CH), 48.5 (CH_2). **(ESI)-MS** calcd for $C_{22}H_{20}NO_2S$ $[M+H]^+$ 362.12 found 361.98.

(E)-4-methyl-N-(4-phenylbut-3-en-1-yl)-N-(propa-1,2-dien-1-yl)benzenesulfonamide 7m was isolated following the **GP-2**. Yield **40%** (55.8 mg, 0.16 mmol). Viscous liquid. **^{1}H NMR (400 MHz, Acetone)** δ = 7.76 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.40 – 7.34 (m, 2H), 7.34 – 7.26 (m, 2H), 7.25 – 7.16 (m, 1H), 6.87 (t, *J* = 6.3 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.22 (dt, *J* = 15.9, 7.1 Hz, 1H), 5.42 (d, *J* = 6.3 Hz, 2H), 3.29 (dd, *J* = 8.2, 6.3 Hz, 2H), 2.57 – 2.26 (m, 5H). **^{13}C NMR (101 MHz, Acetone)** δ = 200.6 (Cq), 144.0 (Cq), 137.5 (Cq), 135.7 (Cq), 131.9 (CH), 129.9 (CH), 128.5 (CH), 127.2 (CH), 127.1 (CH), 126.3 (CH), 126.0 (CH), 99.8 (CH), 87.3 (CH_2), 46.1 (CH_2), 31.6 (CH_2), 20.6 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{21}NNaO_2S$ $[M+Na]^+$ 362.12 found 361.92.

(1R,5R,7R)-6-methylene-7-phenyl-3-tosyl-3-azabicyclo[3.2.0]heptane 6a was isolated following the **GP-3** using **5a** as reagent (35.0 mg, 0.1 mmol). Yield **82%** (28.9 mg, 0.082 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.72 (d, *J* = 8.1 Hz, 2H), 7.39 – 7.27 (m, 4H), 7.26 – 7.17 (m, 3H), 5.05 (t, *J* = 2.4 Hz, 1H), 4.88 (t, *J* = 2.5 Hz, 1H), 3.95 (br, 1H), 3.69 (dd, *J* = 9.7, 4.5 Hz, 2H), 3.42 (br, 1H), 2.89 – 2.65 (m, 3H), 2.44 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 151.5 (Cq), 143.7 (Cq), 142.3 (Cq), 131.9 (Cq), 129.6 (CH), 128.6 (CH), 128.1 (CH), 127.2 (CH), 126.6 (CH), 110.1 (CH_2), 53.8 ($2CH_2$),

53.0 (CH), 45.0 (CH), 43.9 (CH), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{21}NNaO_2S$ $[M+Na]^+$ 362.12 found 362.10

(1R,5R,6R)-6-(4-chlorophenyl)-7-methylene-3-tosyl-3-azabicyclo[3.2.0]heptane 6b was isolated following the **GP-3** using **5b** as reagent (75.0 mg, 0.2 mmol). Yield **53%** (40.1 mg, 0.106 mmol). white solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.72 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.23 (m, 4H), 7.16 (d, *J* = 8.2 Hz, 2H), 5.06 (s, 1H), 4.87 (s, 1H), 3.93 (br, 1H), 3.68 (dd, *J* = 9.7, 4.6 Hz, 2H), 3.43 (br, 1H), 2.85 – 2.62 (m, 3H), 2.45 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 151.1 (Cq), 143.79 (Cq), 140.8 (Cq), 132.3 (Cq), 131.8 (Cq), 129.6 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 110.3 (CH_2), 53.7 (CH_2), 53.7 (CH_2), 52.3 (CH), 45.0 (CH), 43.8 (CH), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{20}ClNNaO_2S$ $[M+Na]^+$ 396.08 found 396.50

(1R,5R,7R)-6-methylene-3-tosyl-7-(4-(trifluoromethyl)phenyl)-3-azabicyclo[3.2.0]heptane 6c was isolated following the **GP-3** using **5c** as reagent (80.9 mg, 0.2 mmol). Yield **67%** (54.5 mg, 0.134 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.75 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.37 (dd, *J* = 8.2, 4.0 Hz, 4H), 5.11 (s, 1H), 4.90 (s, 1H), 4.04 (br, 1H) 3.72 (dd, *J* = 9.8, 3.7 Hz, 2H), 3.47 (br, 1H), 2.88 – 2.67 (m, 3H), 2.46 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 150.6 (Cq), 146.3 (q, *J* = 1.5 Hz, Cq), 143.9 (Cq), 131.6 (Cq), 129.7 (CH), 128.8 (q, *J* = 32.2 Hz, Cq), 128.1 (CH), 127.6 (CH), 125.6 (q, *J* = 3.6 Hz, CH), 124.2 (q, *J* = 271.7 Hz, Cq) 110.8 (CH_2), 53.7 (CH_2), 53.7 (CH_2), 45.0 (CH), 43.7 (CH), 21.6 (CH_3). **^{19}F NMR (564 MHz, $CDCl_3$)** δ = -62.28. **(ESI)-MS** calcd for $C_{21}H_{20}F_3NNaO_2S$ $[M+Na]^+$ 430.11 found 429.95.

(1R,5R,6R)-6-(3-fluorophenyl)-7-methylene-3-tosyl-3-azabicyclo[3.2.0]heptane 6d was isolated following the **GP-3** using **5d** as reagent (71.0 mg, 0.2 mmol). Yield **55%** (39.0 mg, 0.11 mmol). white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.21 (m, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.95 – 6.85 (m, 2H), 5.07 – 5.03 (m, 1H), 4.90 – 4.86 (m, 1H), 3.95 – 3.90 (m, 1H), 3.70 – 3.60 (m, 2H), 3.41 (br, 1H), 2.82 – 2.72 (m, 2H), 2.69 (dd, *J* = 10.0, 5.9 Hz, 1H), 2.43 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 163.1 (d, *J* = 246.0 Hz, Cq), 150.8 (Cq), 144.9 (d, *J* = 6.7 Hz, Cq), 143.9 (Cq), 131.99 (Cq), 130.14 (d, *J* = 8.2 Hz, CH), 129.7 (CH), 128.2 (CH),

123.0 (d, J = 2.8 Hz, CH), 114.0 (d, J = 21.4 Hz, CH), 113.5 (d, J = 21.0 Hz, CH), 110.6 (CH_2), 53.8 (CH_2), 53.76 (CH_2), 52.6 (CH), 45.0 (CH), 43.8 (CH), 21.6 (CH_3). **^{19}F NMR (564 MHz, $CDCl_3$)** δ = -112.87 (q, J = 8.7 Hz). **(ESI)-MS** calcd for $C_{20}H_{20}FNNaO_2S$ $[M+Na]^+$ 380.11 found 379.94.

3-((1R,5R,6R)-7-methylene-3-tosyl-3-azabicyclo[3.2.0]heptan-6-yl)benzonitrile 6e was isolated following the **GP-3** using **5e** as reagent (72.6 mg, 0.2 mmol). Yield **67%** (49.0 mg, 0.134 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.73 (d, J = 8.3 Hz, 2H), 7.60 – 7.50 (m, 2H), 7.51 – 7.29 (m, 4H), 5.13 (br, 1H), 4.90 (br, 1H), 4.04 – 3.96 (m, 1H),3.71 (dd, J = 9.8, 4.2 Hz, 2H), 3.51 – 3.42 (m. 1H), 2.86 – 2.63 (m, 3H), 2.46 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 150.1 (Cq), 143.9 (Cq), 143.7 (Cq), 132.0 (CH), 131.6 (Cq), 130.7 (CH), 130.3 (CH), 129.7 (CH), 129.5 (CH), 128.1 (CH), 118.9 (Cq), 112.7 (Cq), 111.1 (CH_2), 53.7 (CH_2), 53.6 (CH_2), 52.2 (CH), 45.0 (CH), 43.7 (CH), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{21}H_{20}N_2NaO_2S$ $[M+Na]^+$ 387.11 found 387.36.

(1R,5R,7R)-6-methylene-7-(o-tolyl)-3-tosyl-3-azabicyclo[3.2.0]heptane 6f was isolated following the **GP-3** using **5f** as reagent (66.3 mg, 0.19 mmol). Yield **63%** (41.5 mg, 0.120 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.73 (d, J = 8.3 Hz, 2H), 7.45 – 7.29 (m, 3H), 7.23 – 7.07 (m, 3H), 5.16 (br, 1H), 4.95 (br, 1H), 4.16 – 4.07 (m, 1H), 3.73 (t, J = 10.0 Hz, 2H), 3.43 (br, 1H), 2.81 – 2.71 (m, 2H), 2.71 – 2.63 (m, 1H), 2.44 (s, 3H), 2.27 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 150.5 (Cq), 143.7 (Cq), 140.2 (Cq), 135.9 (Cq), 131.8 (Cq), 130.4 (CH), 129.6 (CH), 128.1 (CH), 126.5 (CH), 126.1 (CH), 126.0 (CH), 111.0 (CH_2), 53.9 ($2CH_2$), 50.0 (CH), 44.6 (CH), 43.5 (CH), 21.6 (CH_3), 20.0 (CH_3). **(ESI)-MS** calcd for $C_{21}H_{23}NNaO_2S$ $[M+Na]^+$ 376.16 found 376.00.

(1R,5R,6R)-6-(4-methoxyphenyl)-7-methylene-3-tosyl-3-azabicyclo[3.2.0]heptane 6g was isolated following the **GP-3** using **5g** as reagent (73.9 mg, 0.2 mmol). Yield **80%** (58.8 mg, 0.16 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.72 (d, J = 8.3 Hz, 2H), 7.43 – 7.31 (m, 2H), 7.18 – 7.11 (m, 2H), 6.90 – 6.77 (m, 2H), 5.05 – 4.99 (m, 1H), 4.88 – 4.82 (m, 1H), 3.89 (dq, J = 5.7, 2.9 Hz, 1H), 3.78 (s, 3H), 3.67 (dd, J = 9.7, 5.8 Hz, 2H), 3.46 – 3.36 (m, 1H), 2.82 – 2.72 (m, 2H), 2.68 (dd, J = 9.8, 5.8 Hz, 1H), 2.44 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 158.3 (Cq), 152.1 (Cq), 143.8 (Cq), 134.5 (Cq), 131.7 (Cq), 129.6 (CH), 128.3 (CH), 128.1 (CH), 114.0 (CH), 109.8 (CH_2), 55.3 (CH_3),

53.8 ($2CH_2$), 52.3 (CH), 44.9 (CH), 44.1 (CH), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{21}H_{23}KNO_3S$ $[M+K]^+$ 408.10 found 408.13.

(1R,5R,7R)-6-methylene-7-(pyridin-3-yl)-3-tosyl-3-azabicyclo[3.2.0]heptane 6h was isolated following the **GP-3** using **5h** as reagent (68.2 mg, 0.2 mmol). Yield **59%** (40.7 mg, 0.118 mmol). blue/green solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 5.09 (s, 1H), 4.87 (s, 1H), 4.14 (br, 1H), 3.69 (dd, *J* = 9.8, 6.2 Hz, 2H), 3.52 – 3.41 (m, 1H), 2.97 – 2.67 (m, 3H), 2.44 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 150.6 (Cq), 143.9 (Cq), 131.7 (Cq), 129.7 (CH), 128.1 (CH), 110.9 (CH_2), 53.7 ($2CH_2$), 45.2 (CH), 43.9 (CH), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{19}H_{21}N_2O_2S$ $[M+H]^+$ 341.13 found 341.18.

(1R,5R,7R)-6-methylene-7-phenyl-3-oxabicyclo[3.2.0]heptane 6j was isolated following the **GP-3** using **5j** as reagent (55.0 mg, 0.29 mmol). Yield **49%** (27.0 mg, 0.142 mmol). yellow liquid. **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.40 – 7.20 (m, 5H), 5.04 (dd, *J* = 2.9, 1.9 Hz, 1H), 4.86 (t, *J* = 2.4 Hz, 1H), 4.14 (dd, *J* = 9.1, 7.5 Hz, 2H), 3.87 – 3.79 (m, 1H), 3.66 (dd, *J* = 8.9, 6.2 Hz, 1H), 3.60 (dd, *J* = 9.4, 4.8 Hz, 2H), 3.01 (dt, *J* = 7.5, 5.0 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 153.1 (Cq), 142.9 (Cq), 128.6 (CH), 127.3 (CH), 126.4 (CH), 108.7 (CH_2), 74.0 (CH_2), 73.6 (CH_2), 52.8 (CH), 46.8 (CH), 45.4 (CH). **(ESI)-MS** calcd for $C_{13}H_{14}NaO$ $[M+Na]^+$ 209.09 found 209.95.

(1R,5R,7S)-6-cyclohexylidene-7-phenyl-3-tosyl-3-azabicyclo[3.2.0]heptane 6k was isolated following the **GP-3** using **5k** as reagent (81.5 mg, 0.2 mmol). Yield **66%** (54.2 mg, 0.132 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.74 (d, *J* = 8.2 Hz, 2H), 7.51 – 7.09 (m, 7H), 3.88 (br, 1H), 3.70 (d, *J* = 9.8 Hz, 1H), 3.63 (d, *J* = 9.3 Hz, 1H), 3.54 – 3.41 (m, 1H), 2.69 (ddd, *J* = 15.5, 9.5, 6.4 Hz, 2H), 2.62 – 2.53 (m, 1H), 2.46 (s, 3H), 2.13 – 1.96 (m, 2H), 1.81 – 1.17 (m, 8H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 144.1 (Cq), 143.6 (Cq), 136.3 (Cq), 131.8 (Cq), 129.6 (CH), 129.2 (Cq), 128.5 (CH), 128.1 (CH), 127.1 (CH), 126.2 (CH), 53.9 (CH_2), 53.7 (CH_2), 51.5 (CH), 44.0 CH), 42.4 (CH), 29.3 (CH_2), 29.3 (CH_2), 27.7 (CH_2), 26.8 (CH_2), 26.3 (CH_2), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{25}H_{29}NNaO_2S$ $[M+Na]^+$ 430.18 found 430.46.

(1R,5R,6S)-6-phenyl-7-propylidene-3-tosyl-3-azabicyclo[3.2.0]heptane 6i was isolated following the **GP-3** using **5i** as reagent (36.0 mg, 0.1 mmol). Yield **71%** (25.6 mg, 0.071 mmol). white solid. **^{1}H NMR (400 MHz, Acetone)** δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.25 (m, 4H), 7.24 – 7.13 (m, 1H), 5.38 (tt, *J* = 7.3, 2.3 Hz, 1H), 3.85 (br, 1H), 3.68 – 3.51 (m, 2H), 3.49 (br, 1H), 2.88 – 2.62 (m, 3H), 2.44 (s, 3H), 1.74 – 1.58 (m, 2H), 0.71 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, Acetone)** δ = 143.7 (Cq), 143.6 (Cq), 141.3 (Cq), 132.1 (Cq), 129.6 (CH), 128.5 (CH), 128.1 (CH), 127.1 (CH), 127.0 (CH), 126.2 (CH), 54.4 (CH_2), 53.8 (CH_2), 51.9 (CH), 44.4 (CH), 44.1 (CH), 21.0 (CH_2), 20.6 (CH_3), 12.9 (CH_3). **(ESI)-MS** calcd for $C_{22}H_{25}KNO_2S$ $[M+K]^+$ 406.12 found 406.14.

(1R,5R,7S)-6-benzylidene-7-phenyl-3-tosyl-3-azabicyclo[3.2.0]heptane 6l were isolated as a mixture of Z/E isomers following the **GP-3** using **5l** as reagent (75.0 mg, 0.18 mmol, 1:1 ratio). Yield **39%** (29.3 mg, 0.07 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.74 (d, *J* = 8.1 Hz, 2H), 7.42 – 7.15 (m, 12H), 6.07 (t, *J* = 2.3 Hz, 1H), 4.12 – 4.05 (m, 1H), 3.92 – 3.80 (m, 2H), 3.73 (d, *J* = 10.0 Hz, 1H), 2.95 (td, *J* = 7.7, 2.1 Hz, 2H), 2.77 (dd, *J* = 9.9, 5.7 Hz, 1H), 2.45 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 144.2 (Cq), 143.8 (Cq), 142.5 (Cq), 136.4 (Cq), 131.8 (Cq), 129.7 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 127.7 (CH), 127.5 (CH), 126.8 (2CH), 125.2 (CH), 54.0 (CH_2), 53.7 (CH_2), 52.2 (CH), 45.4 (CH), 45.2 (CH), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{26}H_{25}KNO_2S$ $[M+K]^+$ 454.12 found 454.35. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.72 (d, *J* = 8.3 Hz, 2H), 7.33 – 6.96 (m, 12H), 6.36 (t, *J* = 2.3 Hz, 1H), 4.24 – 4.21 (m, 1H), 3.83 – 3.72 (m, 2H), 3.65 – 3.54 (m, 1H), 2.87 – 2.73 (m, 3H), 2.40 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 143.80 (Cq), 142.8 (Cq), 141.5 (Cq), 135.9 (Cq), 132.1 (Cq), 129.7 (CH), 128.9 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 127.1 (CH), 126.8 (CH), 126.7 (CH), 126.3 (CH), 54.6 (CH_2), 54.1 (CH_2), 53.9 (CH), 46.1 (CH), 45.7 (CH), 21.7 (CH_3). **(ESI)-MS** calcd for $C_{26}H_{25}NaNO_2S$ $[M+Na]^+$ 438.15 found 438.29.

(1R,7R,8S)-7,8-diphenyl-3-tosyl-3-azabicyclo[4.2.0]oct-5-ene 6l' was isolated following the **GP-3** using **5l** as reagent (75.0 mg, 0.18 mmol). Yield **25%** (26.2 mg, 0.063 mmol). white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.28 (m, 6H), 7.25 – 7.16 (m, 6H), 5.29 (s, 1H), 4.44 – 4.27 (m, 2H), 4.23 – 4.18 (m, 1H), 3.35 – 3.26 (m, 2H), 3.24 (t, *J* = 8.4 Hz, 1H), 2.50 – 2.36 (m, 4H). **^{13}C NMR (151 MHz,**

$CDCl_3$) δ = 143.6 (Cq), 141.8 (Cq), 141.0 (Cq), 139.5 (Cq), 134.4 (Cq), 129.8 (CH), 128.7 (CH), 128.6 (CH), 127.5 (CH), 127.1 (CH), 126.9 (CH), 126.6 (CH), 109.8 (CH), 57.5 (CH), 51.0 (CH), 47.7 (CH_2), 45.0 (CH_2), 44.9 (CH), 21.6 (CH_3). **(ESI)-MS** calcd for $C_{26}H_{25}KNO_2S$ $[M+K]^+$ 454.12 found 454.38.

(1R,5S,6S)-6-phenyl-1-tosyl-3-azabicyclo[3.2.0]hept-2-ene 8a was isolated following the **GP-3** using **7a** as reagent (32.7 mg, 0.1 mmol). Yield **59%** (19.3 mg, 0.059 mmol). pale yellow solid**.** **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.74 (d, *J* = 7.5 Hz, 2H), 7.60 (s, 1H), 7.43 – 7.20 (m, 7H), 3.97 (d, *J* = 17.0 Hz, 1H), 3.53 (ddd, *J* = 16.9, 6.4, 2.9 Hz, 1H), 3.32 (t, *J* = 6.5 Hz, 1H), 3.20 (dd, *J* = 12.2, 8.9 Hz, 1H), 2.93 (q, *J* = 8.2 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.45 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 161.4 (CH), 145.5 (Cq), 142.2 (Cq), 133.5 (Cq), 130.1 (CH), 128.9 (CH), 128.8 (CH), 127.2 (CH), 127.0 (CH), 76.0 (Cq), 68.0 (CH_2), 47.2 (CH), 40.4 (CH), 33.5 (CH_2), 21.7 (CH_3).

(1R,5S,6S)-6-(o-tolyl)-1-tosyl-3-azabicyclo[3.2.0]hept-2-ene 8b was isolated following the **GP-3** using **7b** as reagent (64.0 mg, 0.2 mmol). Yield **58%** (37.3 mg, 0.116 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.74 (d, *J* = 8.0 Hz, 2H), 7.64 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.24 (m, 1H), 7.22 – 7.08 (m, 2H), 3.98 (d, *J* = 17.0 Hz, 1H), 3.58 (ddd, *J* = 17.0, 6.4, 2.9 Hz, 1H), 3.39 (t, *J* = 6.3 Hz, 1H), 3.24 – 3.15 (m, 2H), 2.45 (s, 3H), 2.21 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 160.6 (CH), 145.5 (Cq), 139.9 (Cq), 135.3 (Cq), 133.4 (Cq), 130.3 (CH), 130.1 (CH), 128.9 (CH), 126.9 (CH), 126.8 (CH), 126.1 (CH), 76.0 (Cq), 68.2 (CH_2), 45.9 (CH), 36.3 (CH), 33.0 (CH_2), 21.7 (CH_3), 20.1 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{22}NO_2S$ $[M+H]^+$ 340.14 found 340.28.

1R,5S,6S)-6-(4-methoxyphenyl)-1-tosyl-3-azabicyclo[3.2.0]hept-2-ene 8c was isolated following the **GP-3** using **7c** as reagent (36.6 mg, 0.1 mmol). Yield **53%** (18.3 mg, 0.053 mmol). yellow solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.74 (d, *J* = 8.3 Hz, 2H), 7.60 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.17 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.96 (d, *J* = 16.7 Hz, 1H), 3.80 (s, 3H), 3.53 (ddd, *J* = 16.8, 6.3, 2.5 Hz, 1H), 3.27 (t, *J* = 6.4 Hz, 1H), 3.15 (dd, *J* = 12.1, 8.7 Hz, 1H), 2.88 (td, *J* = 8.6, 6.6 Hz, 1H), 2.66 (dd, *J* = 12.1, 8.6 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 158.8 (Cq, CH), 145.5 (Cq), 134.3 (Cq), 133.5 (Cq), 130.0 (CH),129.2 (Cq), 128.9 (CH), 128.1 (CH), 114.1

(CH), 67.9 (Cq), 55.3 (CH3), 39.8 (CH), 33.8 (CH), 29.7 (CH), 21.7 (CH3). **(ESI)-MS** calcd for $C_{20}H_{22}NO_3S$ $[M+H]^+$ 356.13 found 356.06.

(1R,5S,6S)-6-(4-chlorophenyl)-1-tosyl-3-azabicyclo[3.2.0]hept-2-ene 8d was isolated following the **GP-3** using **7d** as reagent (71.0 mg, 0.2 mmol). Yield **38%** (27.0 mg, 0.076 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.73 (d, *J* = 8.0 Hz, 2H), 7.58 (s, 1H), 7.46 – 7.06 (m, 7H), 3.96 (d, *J* = 17.1 Hz, 1H), 3.60 – 3.48 (m, 1H), 3.27 (t, *J* = 6.5 Hz, 1H), 3.14 (dd, *J* = 12.3, 8.8 Hz, 1H), 2.91 (q, *J* = 8.5 Hz, 1H), 2.68 (dd, *J* = 12.3, 8.6 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 161.3 (CH), 145.6 (Cq), 140.7 (Cq), 134.0 (Cq), 133.0 (Cq), 130.1 (CH), 128.9 (CH), 128.9 (CH), 128.4 (CH), 76.0 (Cq), 67.9 (CH_2), 47.1 (CH), 39.8 (CH), 33.5 (CH_2), 20.7 (CH_3). **(ESI)-MS** calcd for $C_{19}H_{19}ClNO_2S$ $[M+H]^+$ 360.08 found 360.10.

3-((1R,5S,6S)-1-tosyl-3-azabicyclo[3.2.0]hept-2-en-6-yl)benzonitrile 8e was isolated following the **GP-2** using **7e** as reagent (45.0 mg, 0.13 mmol). Yield **31%** (14.0 mg, 0.0403 mmol). yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.74 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.58 (m, 2H), 7.56 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 3.99 (d, *J* = 17.1 Hz, 1H), 3.61 (ddd, *J* = 17.0, 6.4, 2.9 Hz, 1H), 3.30 (t, *J* = 6.4 Hz, 1H), 3.14 (dd, *J* = 12.3, 8.7 Hz, 1H), 2.98 (td, *J* = 8.6, 6.5 Hz, 1H), 2.73 (dd, *J* = 12.5, 8.8 Hz, 1H), 2.46 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ = 161.1 (CH), 145.9 (Cq), 143.6 (Cq), 133.1 (Cq), 131.5 (CH), 131.0 (CH), 130.6 (CH), 130.2 (CH), 129.8 (CH), 128.9 (CH), 118.6 (Cq), 112.8 (Cq), 76.0 (Cq), 68.0 (CH_2), 46.8 (CH), 39.8 (CH), 33.3 (CH_2), 21.8 (CH_3). **(ESI)-MS** calcd for $C_{20}H_{19}N_2O_2S$ $[M+H]^+$ 351.12 found 350.84.

(1R,5S,6S)-1-(methylsulfonyl)-6-phenyl-3-azabicyclo[3.2.0]hept-2-ene 8f was isolated following the **GP-3** using **7f** as reagent (26.4 mg, 0.1 mmol). Yield **55%** (14.5 mg, 0.055 mmol). pale brown solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.80 (t, *J* = 2.6 Hz, 1H), 7.40 – 7.14 (m, 5H), 4.29 – 4.09 (m, 2H), 3.41 (t, *J* = 6.2 Hz, 1H), 3.18 – 3.00 (m, 2H), 2.80 – 2.69 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 161.4 (CH), 141.0 (Cq), 129.0 (CH), 127.5 (CH), 127.1 (CH), 75.2 (Cq), 68.4 (CH_2), 46.7 (CH), 41.0 (CH), 37.3 (CH_3), 32.7 (CH_2). **(ESI)-MS** calcd for $C_{13}H_{16}NO_2S$ $[M+H]^+$ 250.09 found 249.95.

(1R,5S,6S)-1-(methylsulfonyl)-6-(o-tolyl)-3-azabicyclo[3.2.0]hept-2-ene 8g was isolated following the **GP-3** using **7g** as reagent (55.5 mg, 0.2 mmol). Yield **49%** (21.3 mg, 0.098 mmol). yellow viscous oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.83 (s, 1H), 7.50 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.34 – 7.23 (m, 1H), 7.23 – 7.09 (m, 2H), 4.30 – 4.14 (m, 2H), 3.53 – 3.44 (m, 1H), 3.30 (td, *J* = 8.8, 6.8 Hz, 1H), 3.08 (dd, *J* = 12.3, 9.0 Hz, 1H), 2.81 – 2.71 (m, 4H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.4 (CH), 139.6 (Cq), 135.2 (Cq), 130.3 (CH), 127.1 (CH), 126.8 (CH), 126.0 (CH), 75.1 (Cq), 68.5 (CH_2), 45.2 (CH), 37.2 (CH_3), 36.9 (CH), 32.2 (CH_2), 20.15 (CH_3). **(ESI)-MS** calcd for $C_{14}H_{18}NO_2S$ $[M+H]^+$ 264.11 found 264.18.

(1R,5S,6S)-6-phenyl-1-(phenylsulfonyl)-3-azabicyclo[3.2.0]hept-2-ene 8h was isolated following the **GP-3** using **7h** as reagent (32.0 mg, 0.1 mmol). Yield **56%** (17.9 mg, 0.056 mmol). pale yellow solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.97 – 7.84 (m, 2H), 7.79 – 7.53 (m, 4H), 7.45 – 7.20 (m, 5H), 4.00 (d, *J* = 17.0 Hz, 1H), 3.53 (ddd, *J* = 17.0, 6.3, 2.9 Hz, 1H), 3.36 (t, *J* = 6.4 Hz, 1H), 3.24 (dd, *J* = 12.1, 8.8 Hz, 1H), 2.97 (td, *J* = 8.6, 6.6 Hz, 1H), 2.72 (dd, *J* = 12.1, 8.5 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 161.3 (CH), 142.1 (Cq), 136.4 (Cq), 134.3 (CH), 129.4 (CH), 128.9 (CH), 128.8 (CH), 127.3 (CH), 127.0 (CH), 76.0 (Cq), 67.9 (CH_2), 47.2 (CH), 40.4 (CH), 33.4 (CH_2). **(ESI)-MS** calcd for $C_{18}H_{18}NO_2S$ $[M+H]^+$ 312.11 found 311.99.

(1R,5S,6S)-1-(mesitylsulfonyl)-6-phenyl-3-azabicyclo[3.2.0]hept-2-ene 8j was isolated following the **GP-3** using **7j** as reagent (34.6 mg, 0.1 mmol). Yield **46%** (15.8 mg, 0.046 mmol). dark yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.47 – 7.19 (m, 5H), 7.01 (s, 2H), 4.14 – 4.05 (m, 1H), 4.01 – 3.90 (m, 1H), 3.53 (t, *J* = 6.2 Hz, 1H), 3.20 (dd, *J* = 12.0, 8.9 Hz, 1H), 2.97 – 2.87 (m, 1H), 2.73 (dd, *J* = 12.0, 8.5 Hz, 1H), 2.65 (s, 6H), 2.34 (s, 3H**). ^{13}C NMR (101 MHz, $CDCl_3$)** δ = 161.3 (CH), 144.0 (Cq), 142.3 (Cq), 140.8 (Cq), 132.8 (CH_2), 131.3 (Cq), 128.8 (CH), 127.1 (CH), 126.9 (CH), 77.9 (Cq), 68.2 (CH_2), 48.0 (CH), 40.0 (CH), 35.44 (CH_2), 23.70 (CH_3), 21.05 (CH_3). **(ESI)-MS** calcd for $C_{21}H_{24}NO_2S$ $[M+H]^+$ 354.14 found 354.02.

(1R,5S,6S)-1-((4-nitrophenyl)sulfonyl)-6-phenyl-3-azabicyclo[3.2.0]hept-2-ene 8k was isolated following the **GP-3** using **7a** as reagent (36.6 mg, 0.1 mmol). Yield **27%**

(10.0 mg, 0.027 mmol). yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 8.41 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 2.7 Hz, 1H), 7.44 – 7.22 (m, 4H), 4.04 (d, *J* = 17.2 Hz, 1H), 3.56 (ddd, *J* = 17.3, 6.4, 2.9 Hz, 1H), 3.38 (t, *J* = 6.5 Hz, 1H), 3.25 (dd, *J* = 12.3, 8.9 Hz, 1H), 3.00 (td, *J* = 8.7, 6.6 Hz, 1H), 2.74 (dd, *J* = 12.3, 8.6 Hz, 1H). **^{13}C NMR (75 MHz, Acetone)** δ = 159.8 (CH), 151.4 (Cq), 142.7 (Cq), 142.3 (Cq), 130.7 (CH), 128.6 (CH), 126.9 (CH), 126.8 (CH), 124.6 (CH), 76.1 (Cq), 67.7 (CH_2), 46.8 (CH), 40.1 (CH), 32.9 (CH_2). **(ESI)-MS** calcd for $C_{18}H_{17}N_2O_4S$ $[M+H]^+$ 357.09 found 356.97.

(1R,5S,6S)-1-((4-chlorophenyl)sulfonyl)-6-phenyl-3-azabicyclo[3.2.0]hept-2-ene 8i was isolated following the **GP-3** using **7i** as reagent (34.1 mg, 0.1 mmol). Yield **68%** (23.5 mg, 0.068 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.80 (d, *J* = 8.6 Hz, 2H), 7.61 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.43 – 7.20 (m, 5H), 4.01 (d, *J* = 17.1 Hz, 1H), 3.56 (ddd, *J* = 17.2, 6.3, 2.9 Hz, 1H), 3.33 (t, *J* = 6.4 Hz, 1H), 3.21 (dd, *J* = 12.2, 8.8 Hz, 1H), 2.96 (td, *J* = 8.7, 6.6 Hz, 1H), 2.71 (dd, *J* = 12.2, 8.6 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ = 161.0 (CH), 141.9 (Cq), 141.3 (Cq), 134.9 (Cq), 130.3 (CH), 129.8 (CH), 128.8 (CH), 127.3 (CH), 126.9 (CH), 76.1 (Cq), 68.0 (CH_2), 47.2 (CH), 40.4 (CH), 33.4 (CH_2). **(ESI)-MS** calcd for $C_{18}H_{17}ClNO_2S$ $[M+H]^+$ 346.07 found 346.02.

(1R,5S,6S)-1-(naphthalen-1-ylsulfonyl)-6-phenyl-3-azabicyclo[3.2.0]hept-2-ene 8l was isolated following the **GP-3** using **7l** as reagent (72.5 mg, 0.2 mmol). Yield **42%** (30.3 mg, 0.084 mmol). pale brown solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 8.45 (s, 1H), 8.07 – 7.88 (m, 3H), 7.83 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.76 – 7.56 (m, 3H), 7.40 – 7.20 (m, 5H), 3.97 (d, *J* = 16.9 Hz, 1H), 3.54 (ddd, *J* = 16.8, 6.3, 2.8 Hz, 1H), 3.43 (t, *J* = 6.4 Hz, 1H), 3.28 (dd, *J* = 12.2, 8.8 Hz, 1H), 2.96 (td, *J* = 8.7, 6.5 Hz, 1H), 2.72 (dd, *J* = 12.2, 8.6 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 161.3 (CH), 142.2 (Cq), 135.5 (Cq), 133.5 (Cq), 132.1 (Cq), 130.9 (CH), 129.7 (CH), 129.7 (CH), 129.5 (CH), 128.8 (CH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 127.0 (CH), 123.1 (CH), 77.3 (Cq), 68.0 (CH_2), 47.3 (CH), 40.5 (CH), 33.6 (CH_2). **(ESI)-MS** calcd for $C_{22}H_{20}NO_2S$ $[M+H]^+$ 362.12 found 361.93.

(1R,6R,7S)-7-phenyl-1-tosyl-3-azabicyclo[4.2.0]oct-2-ene 8m was isolated following the **GP-3** using **7m** as reagent (46.0 mg, 0.13 mmol). Yield **26%** (13.5 mg, 0.034 mmol). white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 8.21 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.50

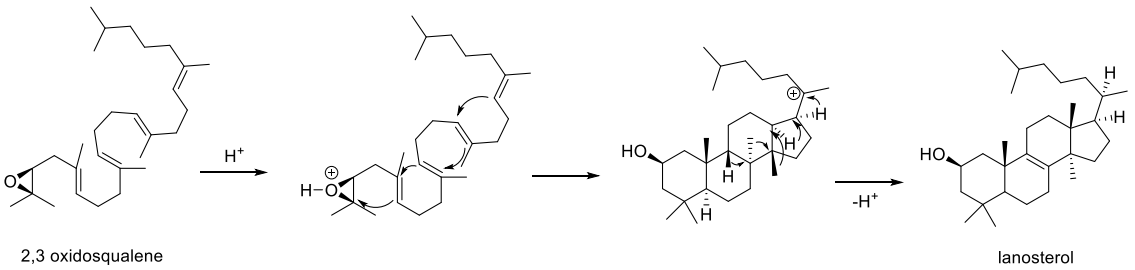
– 7.11 (m, 8H), 3.79 (dd, *J* = 18.3, 5.6 Hz, 1H), 3.67 – 3.53 (m, 1H), 3.32 (t, *J* = 4.4 Hz, 1H), 3.21 – 3.06 (m, 2H), 2.61 – 2.48 (m, 1H), 2.45 (s, 3H), 1.55 – 1.44 (m, 1H), 0.95 – 0.80 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 157.7 (CH), 145.5 (Cq), 142.0 (Cq), 133.4 (Cq), 130.1 (CH), 129.2 (CH), 128.8 (CH), 127.2 (CH), 127.1 (CH) (CH), 56.9 (Cq), 45.1 (CH_2), 40.1 (CH), 36.3 (CH), 34.0 (CH_2), 21.8 (CH_3), 19.8 (CH_2). **(ESI)-MS** calcd for $C_{20}H_{22}NO_2S$ $[M+H]^+$ 340.14 found 340.20.

4 Intermolecular cascade reactions triggered by photoactivation of cumulated double bond *via* energy transfer.

From this chapter: Andrea Serafino, Maurizio Chiminelli, Davide Balestri, Luciano Marchiò, Franca Bigi, Raimondo Maggi, Max Malacria and Giovanni Maestri*. ***Chem. Sci.***, 2022,**13**, 2632-2639. DOI https://doi.org/10.1039/D1SC06719B

4.1 Introduction

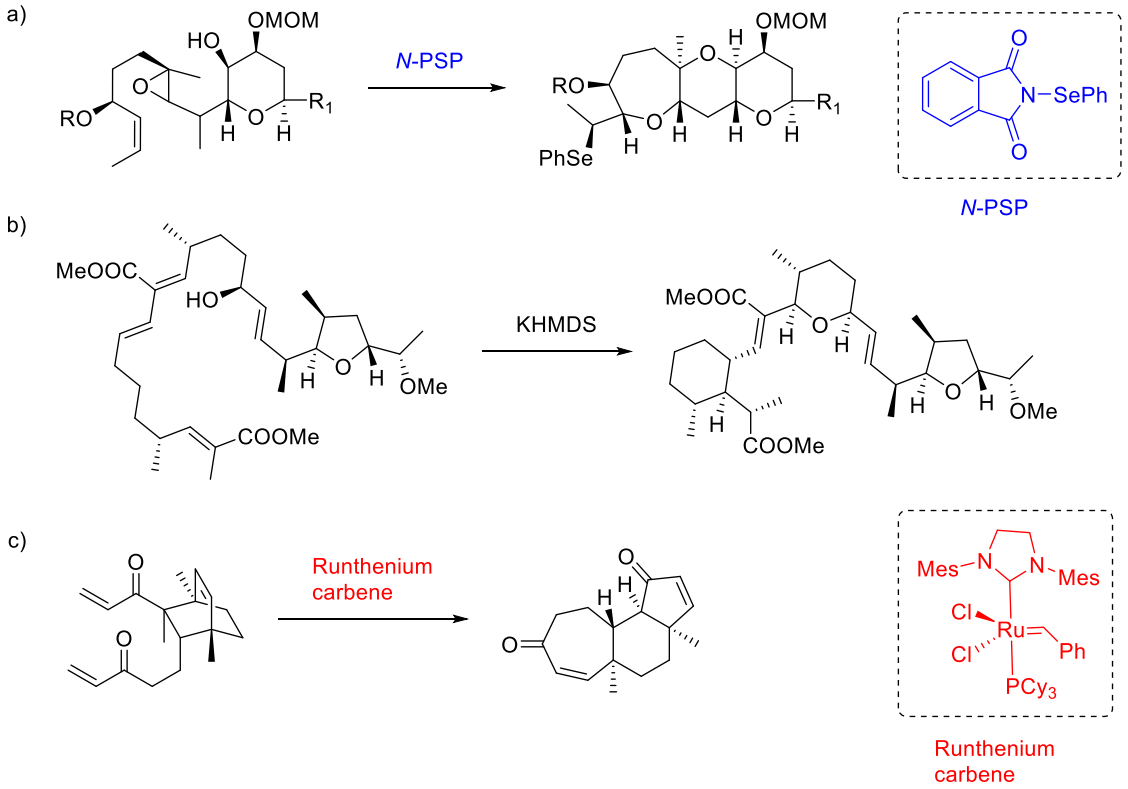
In the modern organic chemistry, the concept of atom economy has become increasingly important. In an idealized concept of chemical reaction only atoms of reagents must be present in the products. It is obvious, therefore, that the use of stoichiometric reagents or leaving groups represent a waste to be disposed of. Another key concept concerns the number of steps, and of purifications, that must be minimized. The combination of unsaturations and cascade reactions certainly play a role to solve this problem. Nature, which is a master in this field, provides us a myriad of interesting examples[89]. Among these, the biosynthesis of tetracyclic lanosterol from linear polyunsaturated 2,3-oxidosqualene is remarkable (Scheme 38).



Scheme 38 biosynthesis of lanosterol.

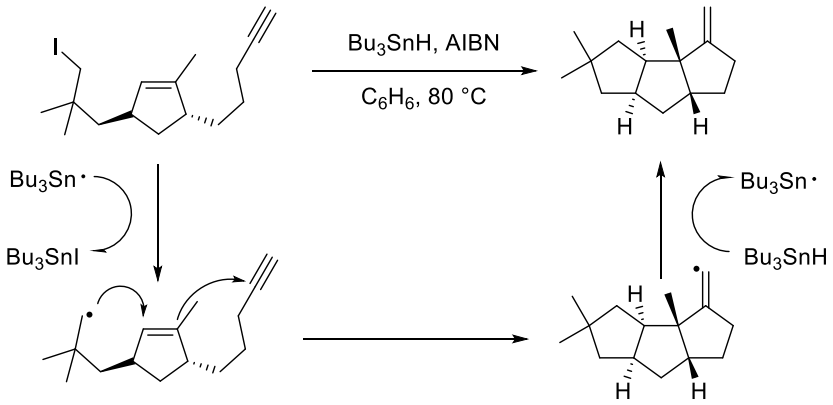
Since the first cascade reaction was reported for the preparation of tropinone in 1917 by Robinson[90], the development of new cascade reactions has stimulated the fantasy of chemists until today[91].

Many method to trigger a cascade reaction exist. Electrophilic (Scheme 39, a)) and nucleophilic (Scheme 39, b)) initiations were largely studied since twenties of the past century. In the last three decades then, the rapid development of organometallic chemistry provided a series of new complementary approaches to cascade reactions[92] (Scheme 39, c)).



Scheme 39 selected examples of cascade reactions. a) electrophilic cascade from total synthesis of hemibrevetoxin B by Holton[93]. b) nucleophilic cascade from total synthesis of tetronasin by Ley. c) Ruthenium catalyzed cascade metathesis cyclization in the total synthesis of cyanthiwigin U by Pfeiffer and Phillips[94].

The radical initiation was considerably less thorough because of the intrinsic difficulty to control unstable radical intermediates, even if there are some interesting examples. In the total synthesis of (±) hirsutene, Curran and Chen used a radical domino reaction to afford the target molecule in one step from an opportunely decorated cyclopentene[95] (scheme 40). However, in a few years, a large number of researches in this field were published[96–98].



Scheme 40 key step in the total synthesis of hirsutene.

Recent progresses in radical chemistry initiated by single electron transfer (SET) have led to fascinating developments in domino reactions raising the bar ulteriorly[99]. These processes can be activated using visible light with a suitable photoredox catalyst[10,100]. In the same way the use of visible light combined with an opportune sensitizer can generate highly reactive radical intermediates[101].

Photoactivation of C-C double bonds via eT led to the formation of reactive diradical species that can trigger cascade reactions with total atom economy. However, the activation of isolated double bond can be not trivial. This issue can be addressed thanks to a conjugated π-unit. Thanks to the conjugation, this unsaturated unit, which can be a styrene, diene or carbonyl group among the others, delocalized the spin density and this stabilized the intermediate. The activation of cumulated double bonds via eT is much more challenging because of the formation of an unstable vinyl radical (Figure 14). For this reason, only thermal and transition metal catalyzed activation of allenes was previously reported.

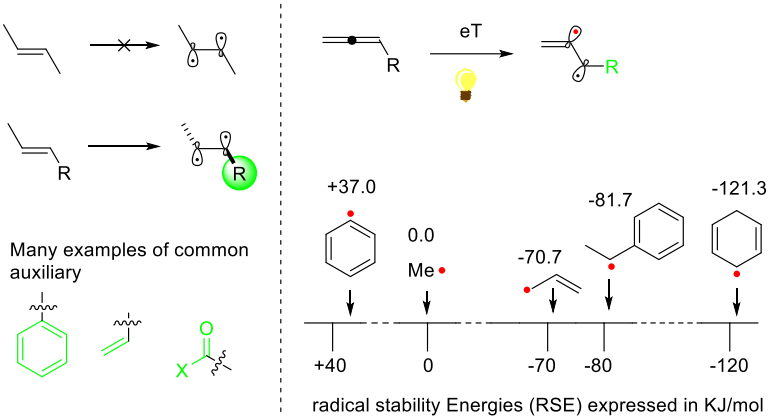
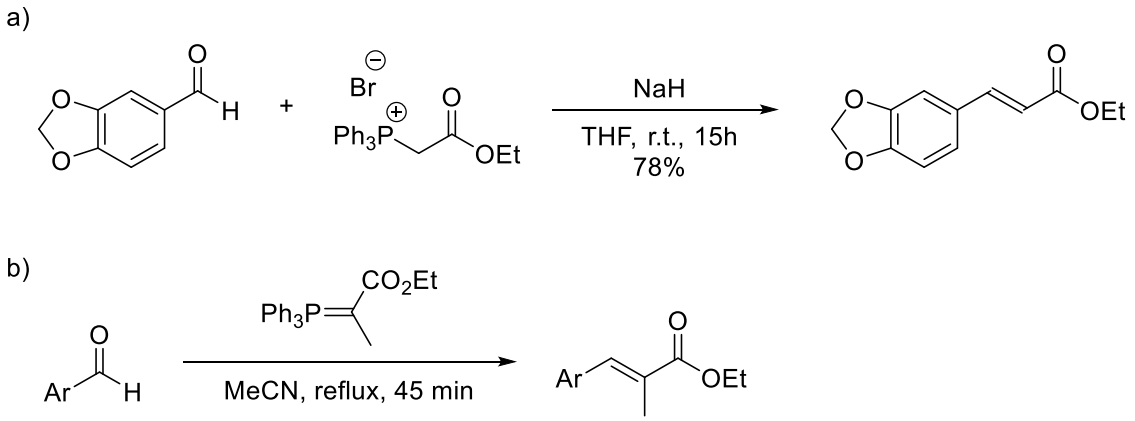


Figure 14 examples of auxiliary group and a series of carefully selected radical with its energy[116].

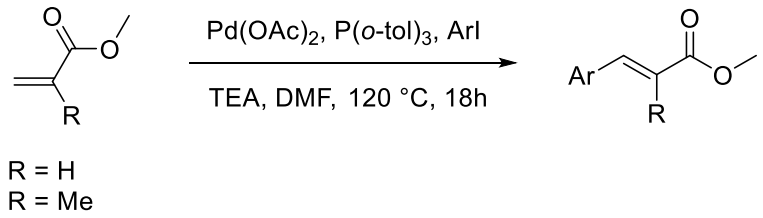
4.2 Results and discussion

Synthesis of substrates required a huge synthetic effort. Several olefination and coupling methods were employed to obtain ester precursors depending on the available chemicals. Wittig reaction, with phosphorous ylide usually prepared in situ, worked well for preparing electron rich cinnamic esters (Scheme41, a)). The use of a secondary ylide, however, required the isolation of it to obtain a satisfactory yield (Scheme 41, b)).



Scheme 41 synthesis of esters precursors via wittig olefination.

The use of Heck coupling was extensively used for the preparation of cinnamic esters. β-elimination step showed high selectivity even whit α-methyl group delivering the desired products in good yield (Scheme 42).

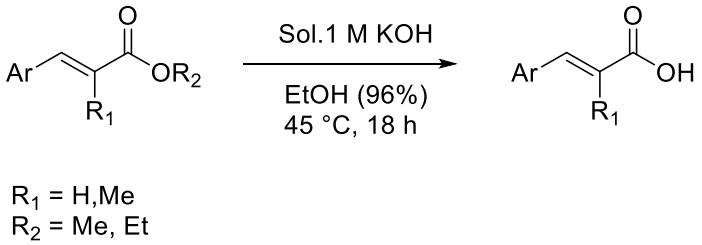


Scheme 42 Heck type coupling for the preparation of cinnamic esters.

Titanium-enolate based asymmetric aldol condensations using aldehydes and α-haloacetates was employed for the synthesis of α-halogenated cinnamic esters[102] (Scheme 43).

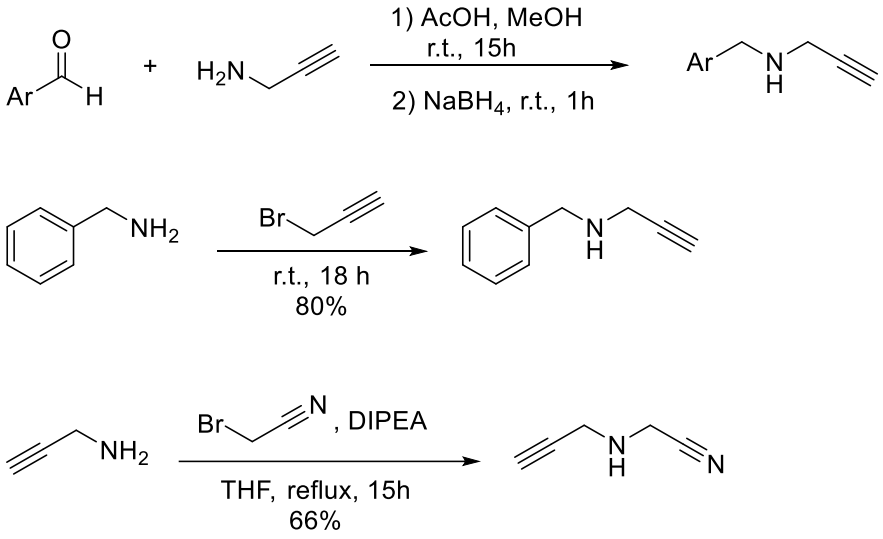
Scheme 43 synthesis of α-halogenated esters.

The corresponding cinnamic acids were smoothly achieved by basic hydrolysis of the corresponding esters (Scheme 44).



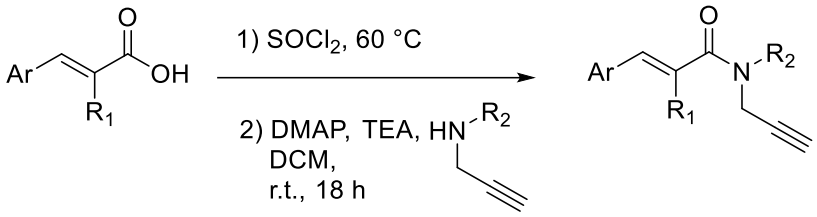
Scheme 44 hydrolysis of esters.

Alkylated propargylamines were obtained using classical reductive amination and nucleophilic substitution (Scheme 45).



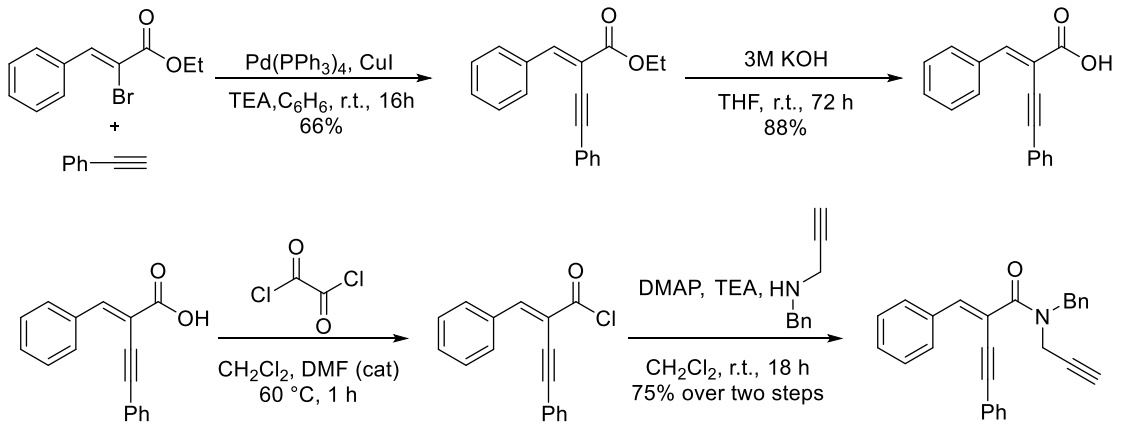
Scheme 45 synthesis of alkylated propargylamines.

1,6 Enynes were prepared by chlorination of cinnamic acids using thionyl chloride and following nucleophilic substitution with secondary amines (Scheme 46).



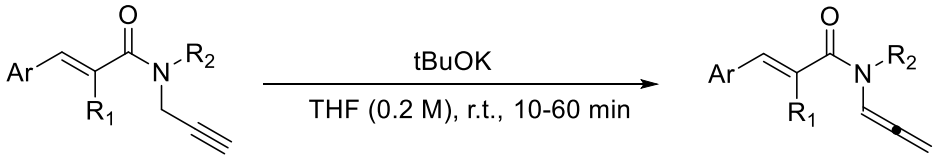
Scheme 46 synthesis of 1,6 enynes

1,6 enyne precursor of **9c** was obtained in five streps from α-Bromo-cinnamic ester. Through Sonogashira coupling, a phenyl acetylene arm was inserted. Subsequent hydrolysis and chlorination using oxalyl chloride afforded the corresponding cinnamoyl chloride. The last step was the nucleophilic substitution with a secondary amine (Scheme 47).



Scheme 47 synthesis of enyne precursor of 9c.

1,6 enallenes were obtained by isomerization of terminal alkyne (Scheme 48). However, this step was the bottleneck in the synthesis of enallenes.



Scheme 48 isomerization of terminal alkynes.

Isomerization process had demonstrated to be strongly dependent from the nature of the attached functional groups. Below there is a table of enynes that failed to isomerize under standard condition (Figure 15).

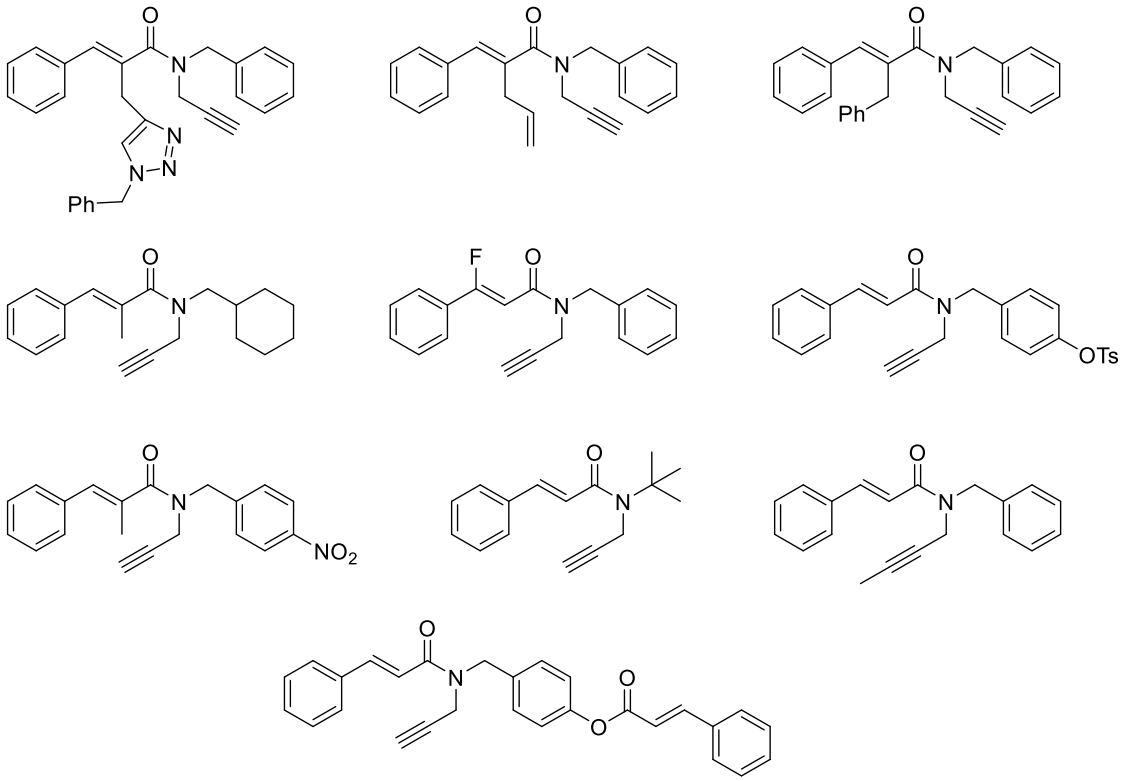
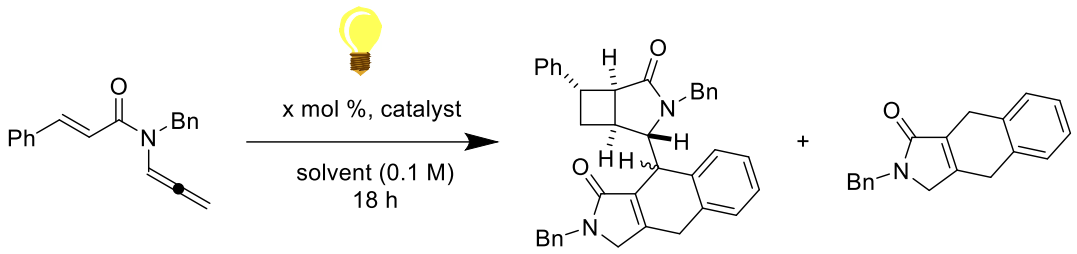


Figure 15 collection of 1,6 enynes unable to isomerize under standard condition.

In a standard experiment for the optimization of dimerization of cinnamoylallenamides **9**, a solution of **9a** and an Ir(III) catalyst in DMF (0.1 M) was placed in a 5 mm NMR tube and degassed using a standard freezing-pump procedure. The solution was subsequently irradiated by a 14W household white LED strip (spectral window from 350 to 750 nm) for 18 hours (table 2).

The use of $Ir(p\text{-}F\text{-}ppy)_3$ delivered **10a** in 28% yield. The yield of **10a** raised to 45% using $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$. The best result was achieved using $Ir(ppy)_3$ as catalyst with a 54% yield of **10a**. The use of $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ afforded only traces of **10a**. The poor (15%) and moderate (25%) yields obtained in toluene and DCM respectively show that a polar solvent was necessary. The lack of conversion in EtOH is probably due to the poor solubility of the reagent and the catalyst in this media. Presence of water in the reaction media does not significantly affect the yield but, in contrast, the presence of molecular oxygen, which probably compete with substrates quenching the triplet state of the photocatalyst, brings down the yield.

. The use of $[Ir(dtbbpy)(ppy)_2]PF_6$, or other common organic photocatalyst failed to deliver **10a** and no conversion of allenene was observed. The same result was obtained without catalyst or irradiation.



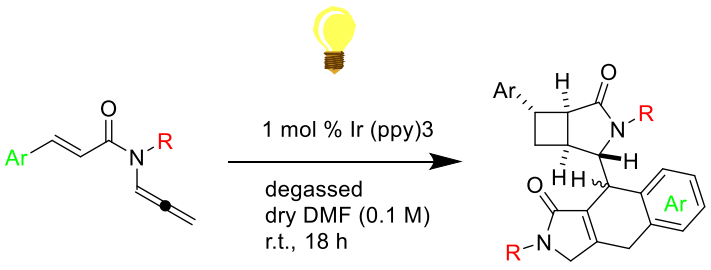
9a 10a 10'a

entry	Catalyst (1 mol%)	Solvent (0.1 M)	Yield[a] 6a
1	$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	DMF	45%
2[b]	$Ir(ppy)_3$	DMF	47%
3	$[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$	DMF	traces
4	$[Ru(bpy)_3]Cl_2$	DMF	/
5[c]	Ir(p-F-ppy)$_3$	DMF	28%
6	TPT+	DMF	/
7	$[Ir(dtbbpy)(ppy)_2]PF_6$	DMF	/
8	$Ir(ppy)_3$	DMF	54%
9[d]	$Ir(ppy)_3$	DMF	31%
10[e]	$Ir(ppy)_3$	DMF	/
11	Eosin y	DMF	/
12	riboflavin	CH_3CN	/
13	Thioxanthen-9-one	DMF	/
14[c]	$Ir(ppy)_3$	dioxane	32%
15[c]	$Ir(ppy)_3$	toluene	15%
16[c]	$Ir(ppy)_3$	DCM	25%
17	$Ir(ppy)_3$	MeCN	48%
18	$Ir(ppy)_3$	ETOH	/
19	$Ir(ppy)_3$	DMSO	52%
20	$Ir(ppy)_3$	DMF/DIPA 4:1	31%
21	$Ir(ppy)_3$	DMF/$H_2$0 19:1	52%

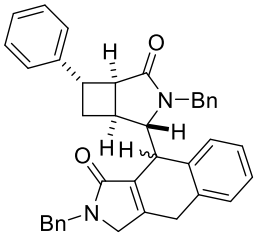
Table 2 [a] isolated yield, [b] 2 mol % of photocatalyst, [c] ^{1}H NMR yield using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard, [d] in presence of oxygen, [e] without irradiation.

With the optimized condition in hand, we tested the generality of this reaction (scheme 49). Various alkyl groups on the nitrogen atom were well tolerated by the dimerization. Products **10b** and **10c** were recovered in moderate to good yield (36% and 48% respectively). The enallenamide **9d** that incorporated aniline afforded product **10d** as a single diastereomer, even if in low yield (17%). On the contrary, a *N*-cyclopropyl arm

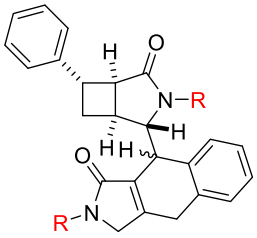
worked well, affording **10e** in 54% yield. Unfortunately, due to a direct isomerization from propargyl amide to ynamide[103], a substrate bearing a tert-butyl group on the nitrogen atom was not achieved. Switching to functionalization of the styryl fragment, we began from the symmetric *para*-substituted arene. Strongly electron withdrawing groups, like trifluoromethyl, were tolerated, although the product was recovered in poor yield. A better result was obtained with a chloride substituent (32% yield). Quite surprisingly[104], an aryl bromide was well tolerated in the sequence, and the corresponding product was isolated in good yield (44%) furnishing a versatile functionalized dimer **10g**. A comparable yield was obtained with an electron donating methoxy group (47%). A methyl group in the *orto*-position of aryl gave a good yield (61%). The meta substituted aryl substrates **9j** and **9k** delivered a mixture of product in ca. 1:1 ratio because of the absence of symmetry in the aryl fragment. The absence of regiochemical control due to steric factors suggest that the aryl C-H functionalization is likely an intramolecular homolytic substitution. However, the sum of both regioisomers delivered a very good yield (54% and 63%). The use of a reagent with an electron-rich protected catechol arm led to a single regioisomer of the dimer in good yield (**10l**, 61%), which has a fused tetracyclic arm often encountered in bioactive molecules, such as popular topoisomerase inhibitors etoposide and phodophillotoxin[105,106].



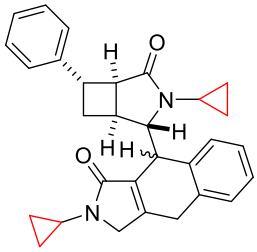
9 10



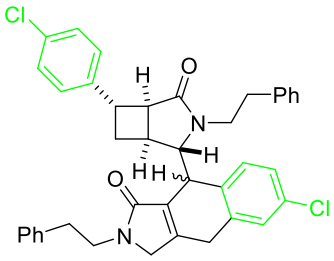
10a 54%



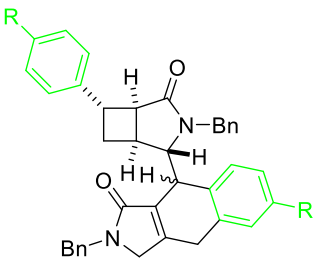
10b R = nC9H19 36%
10c R = CH_2CH_2Ph 48%
10d R = Ph 17%



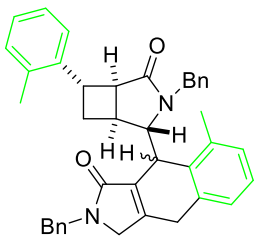
10e 54%



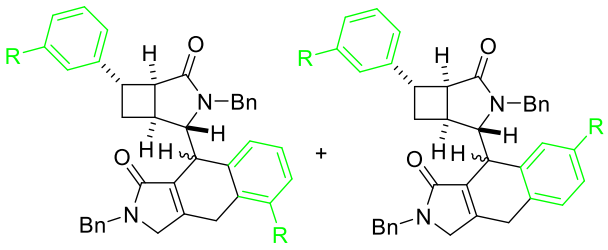
10f 32%



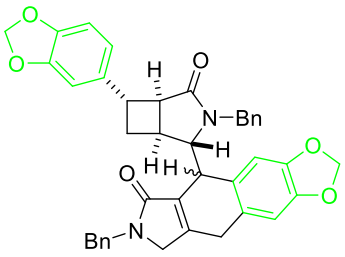
10g R = Br 44%
10h R = OMe 47%



10i 61%



10j R = Me 54% ratio 1:1
10k R = OMe 54% ratio 1:1



10l 61%

Scheme 49 scope of dimeric compounds 10.

In almost all cases (except for **10d**) two diastereomers were recovered in ca. 1:0.8 ratio. The relative configuration of stereocenters in the less abundant isomer **10a** was determined by XRD analysis (Figure 16).

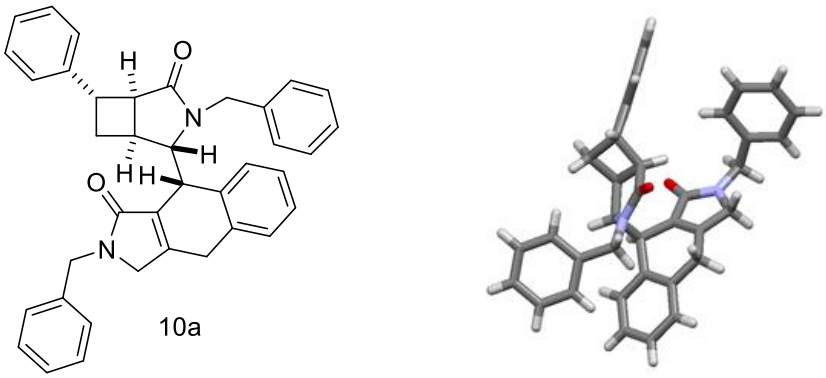


Figure 16 ORTEP of 10a.

The relative configuration of stereocenters in the most abundant isomer **10a'** was deduced by comparison of NOE correlations. In order to obtain information about the chemical environmental of proton 8' we selected bromine substituted dimers in which the latter was clearly visible in the spectrum. The 3.2.0 subunit showed identical cross-peak. Correlation between aromatic proton 8' and benzylic proton 3'' is present in **10g** (Figure 17, *in blue*). It does not exist in **10g'** spectra, in this case the proton 8' was correlated to headbridge proton 1 (Figure 18, *in blue*). The absence of dipolar coupling between proton 9' and proton 1 in **10g**', which is found in **10g**, show that the two protons are on opposite faces of the dimer. This is probably due to the limited stereocontrol in the intermolecular step.

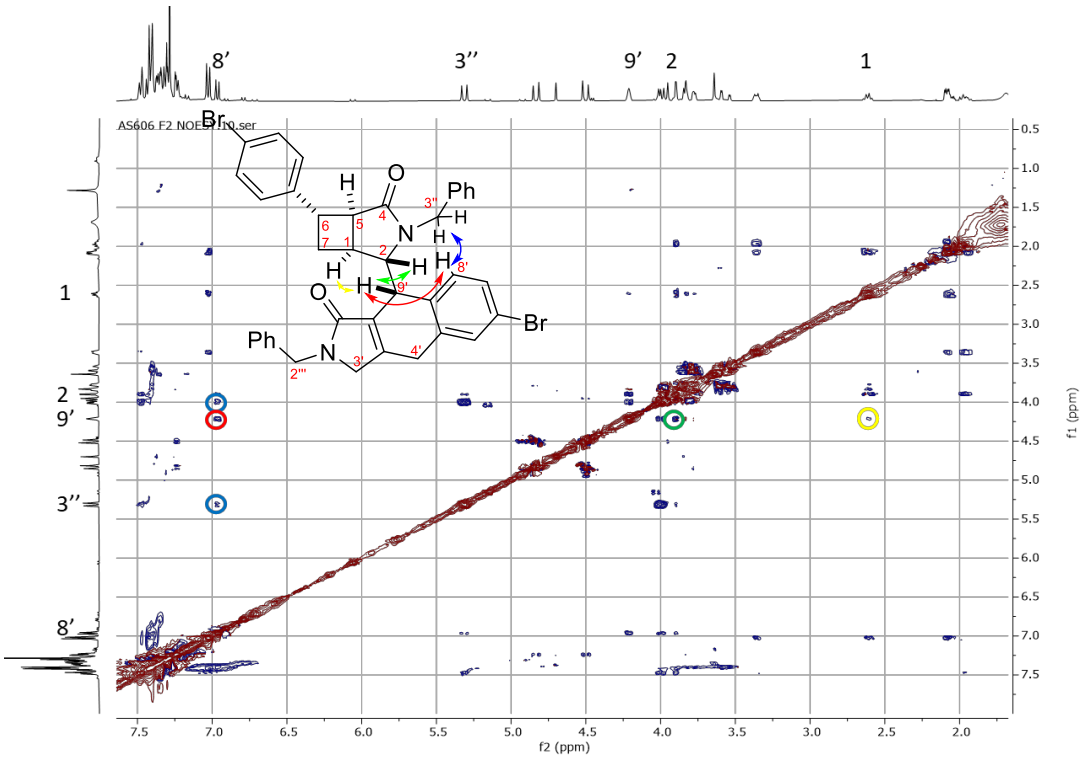


Figure 17 NOESY experiment of less abundant isomer **10g** whose configuration was the same of **10a (Figure 16)**.

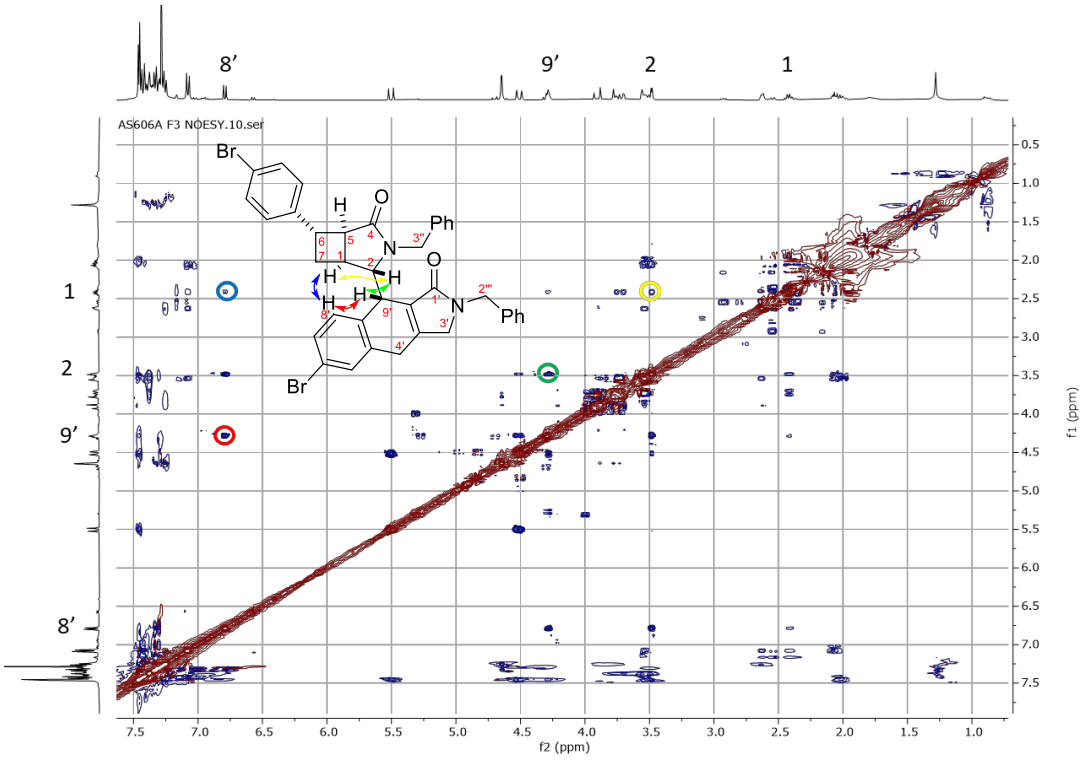
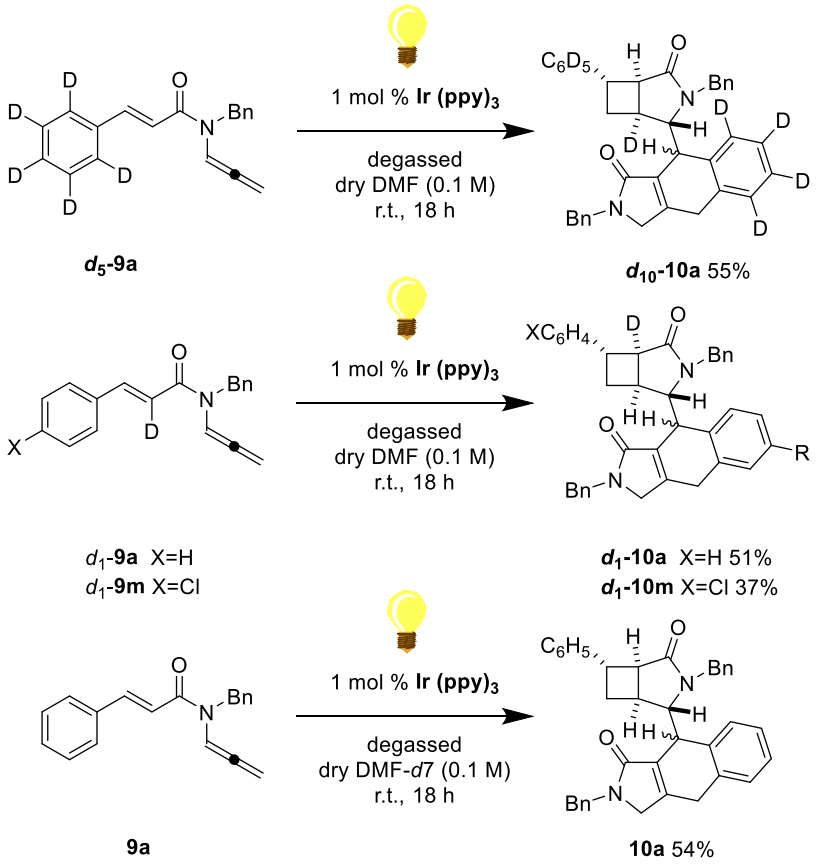


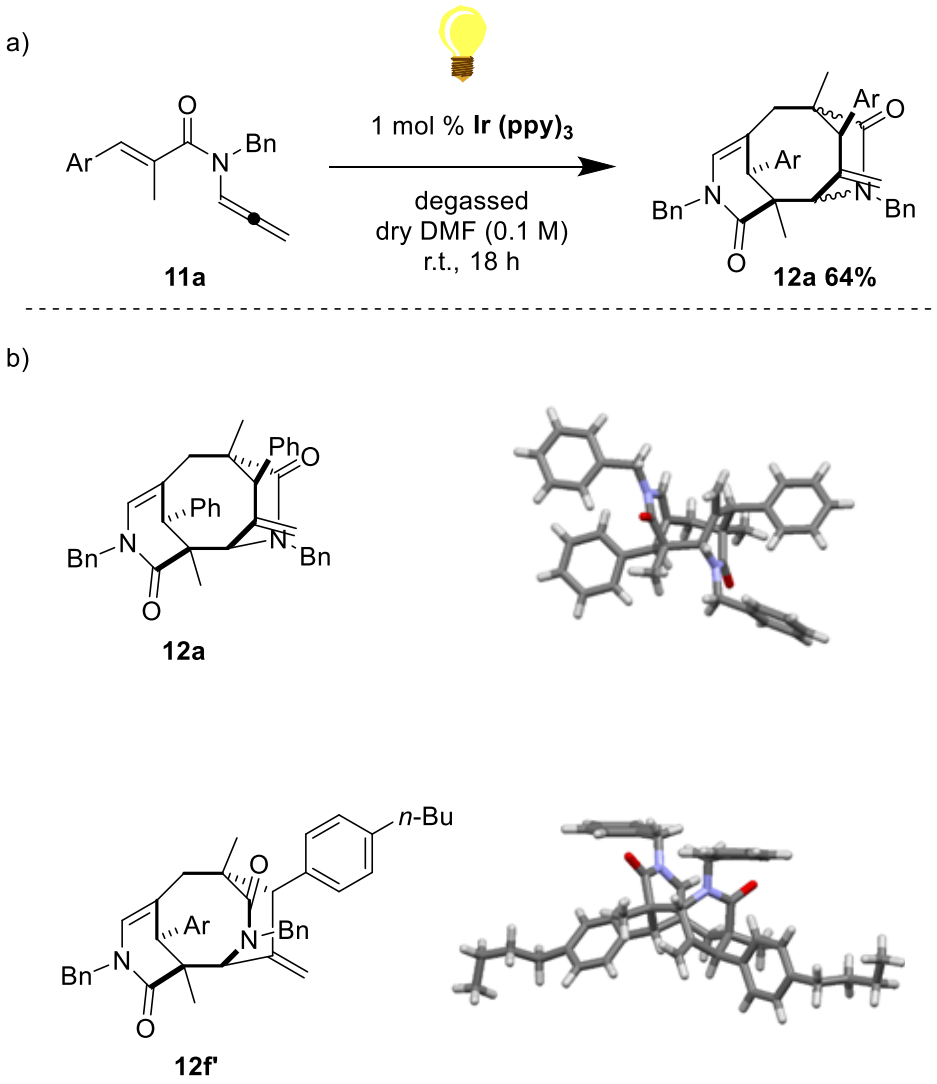
Figure 18 NOESY experiment of most abundant isomer **10g'** whose configuration was assigned on the basis of this spectrum.

In the multistep reaction that delivered dimer **10** from enallenamide **9**, several HATs occurred. We performed experiments with deuterium-labelled reagents to rationalize them. The aryl-deuterated anellenamide ***d*$_5$-9a** was prepared from commercially available pentadeuterated bromobenzene using the same procedure above reported. The reaction under standard condition afforded product ***d*$_{10}$-10a** in 55% yield. HRMS analysis confirmed the presence of the target molecular weight. NMR analysis clearly showed that the headbridge position away from carbonyl in the 3.2.0 subunit was extensively labelled, as expected. The next step forced us to investigate the destiny of proton originally bonded to the α position of carbonyl group in tricyclic subunit. We synthetized an α-deutero-cinnamic via Knoevenagel condensation using D_2O as deuterium source. Enallenamide ***d*$_1$-9a** was obtained as described. The reaction of ***d*$_1$-9a** delivered product ***d*$_1$-10a** in 51% yield. Surprisingly NMR and HRMS evidenced the presence of only one deuterium atom in the product, next to carbonyl in the [3.2.0] bycicle. We recovered the photocatalyst at the end of the reaction and checked if its ligands underwent H/D scrambling[107]. We performed the reaction in DMF-d_7 using **9a** as reagent, but no labelling occurred (54% of **10a**). Puzzled by these observations, we synthesized ***d*$_1$-9m** to confirm the result. The reaction gave mono-deuterated dimer ***d1*-10m** (37%). **10'm** was also isolated from this reaction, but deuterium was not observed (Scheme 50).



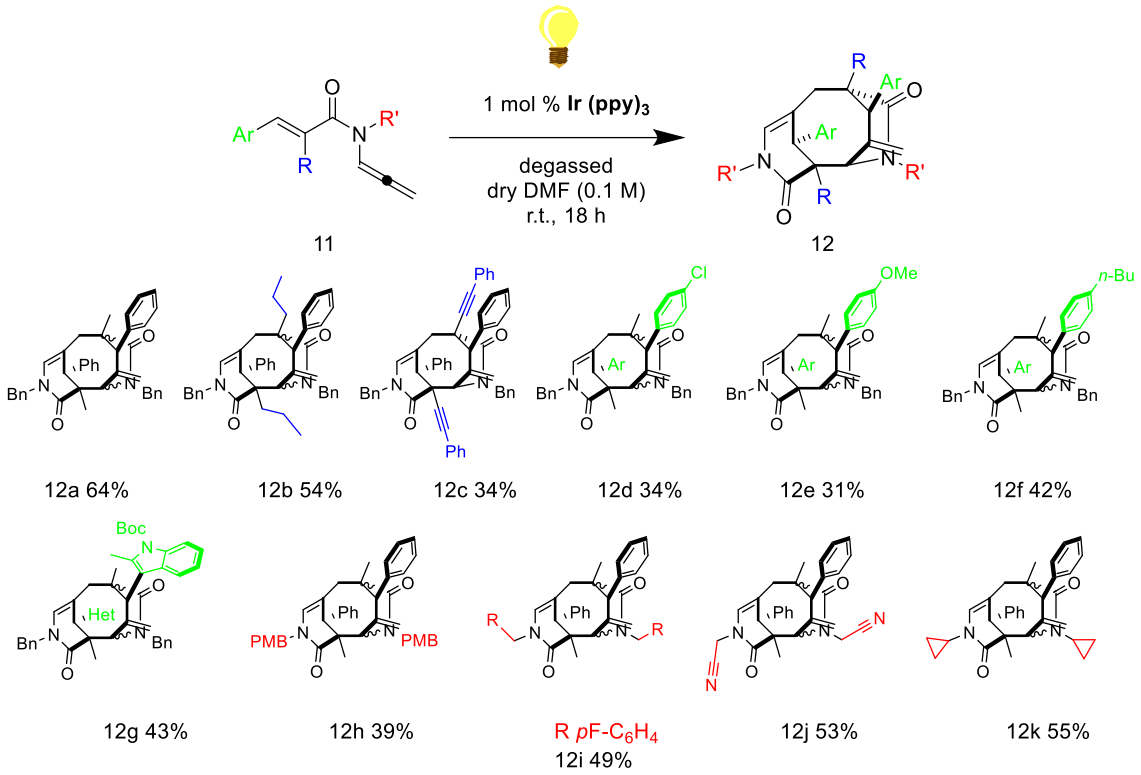
Scheme 50 deuterium labelling experiments.

Intrigued by this oddity, we tested **11a** which had a methyl group instead of a proton in α to the carbonyl group. The reaction afforded a mixture of products (scheme 51 a)) that X-Ray analysis identified as two diastereomers of the bridged tricycle **12a** (64% yield). The two diastereomers of **12a** differed by the relative configuration of one lactam with respect to the central cyclooctane (scheme 51 b)).



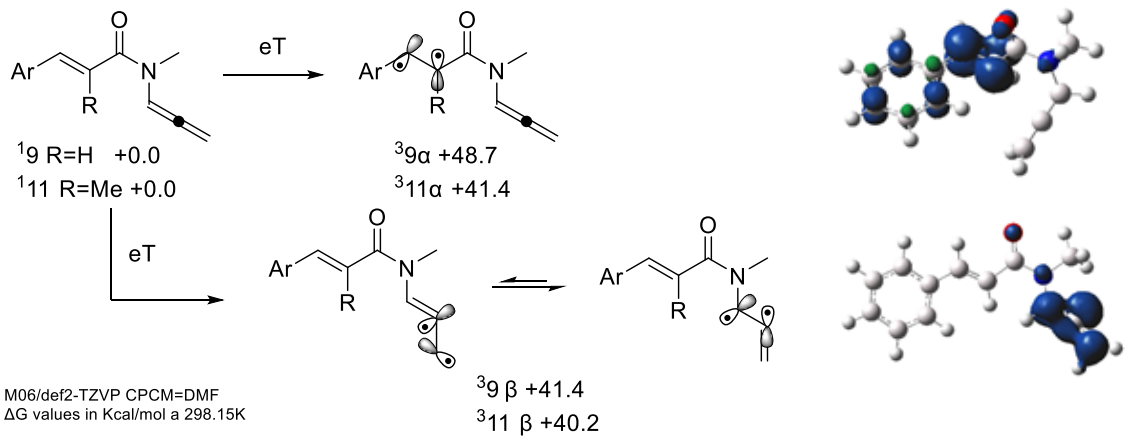
Scheme 51 a) dimerization reaction of allenamides 11. b) ORTEP of taxanes-like tricycles 12.

Given the interest that these complex structures aroused, due to the similarity with the precious taxanes[108–110], we decided to test the generality of this new cascade (scheme 52). Replacing the methyl group with a more hindered n-propyl group led to **12b** (54% yield). Even an alkyne motif was tolerated, affording **12c** in moderate yield (36%). The isolation of only one isomer suggests that staking between aryl and phenylacetylene arm directed the process. Switching the substitution of the aryl unit, an electron-withdrawing chlorine or an electron donating methoxy equally had a negative impact on the yield (**12d-e** 31-34%). A better result was achieved with an alkyl chain (**12f** 42%). Using Boc-protected indole, the reaction afforded **12g** in 43% yield. Finally, the effect of N-substitution was investigated. The use of a *para*-methoxybenzyl group fragment led to formation of **12h** in 39% yield. A better result was obtained using *para*-fluorobenzyl and cyanomethylene fragments (**12i-j** 53-49%). N-cyclopropyl enallenamide gave the corresponding product in 55% yield.



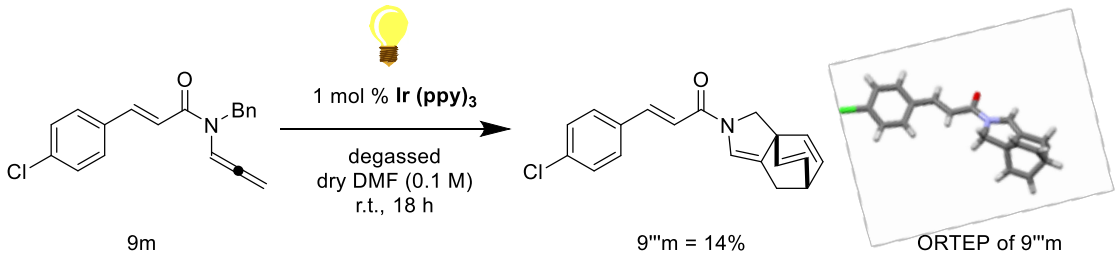
Scheme 52 scope of taxanes-like tricyclic cyclooctanes

The redox potentials for the $Ir(ppy)_3$ were reported in the introductive section (Ir(III)*/Ir(II) 0.31 V and Ir(IV)/Ir(III)* -1.73 V vs SCE). DFT calculations provide us very positive ΔG values for the redox process that involved cinnamoylallenamide and photocatalyst. For the calculation a derivative of 9a, in which a methyl group replaced benzyl group, chosen in order to keep down the computational cost, was selected. In particular, calculated ΔG for the oxidation of the selected substrate by $Ir(ppy)_3$ was +30.8 Kcal/mol while the calculated ΔG for the reduction of the same substrate was +5.6 Kcal/mol. The calculated triplet energy of ^{3}**9a** (+48.7 Kcal/mol) and ^{3}**11a** (+41.4 Kcal/mol) match that of $Ir(ppy)_3$ (calculated triplet state 55.1 Kcal/mol, experimental triplet state 56.3 Kcal/mol). The geometries and spin-densities of both activated substrates reflect the literature. However, a more convenient eT process was unexpectedly found. Further studies, therefore, evidenced that activation of the proximal double bond of acyl allenamide in both enallenamides had a lower energy cost (41.4 Kcal/mol for ^{3}**9a** and 40.2 Kcal/mol for ^{3}**11a**). The instability of vinyl radical was largely balanced by the high stability of partial diallyl character of the radical in α to nitrogen atom (Scheme 53).



Scheme 53 triplet energies of substrates 9 and 11

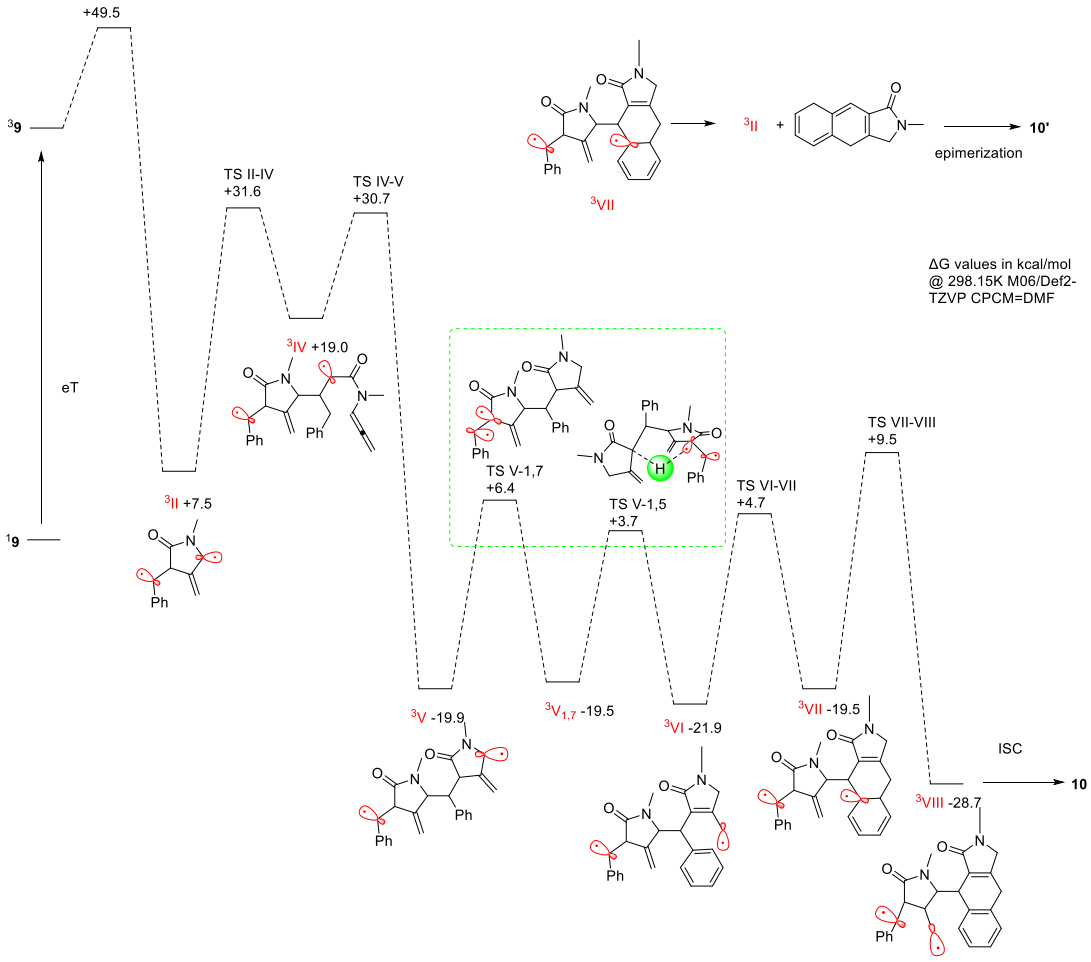
An experimental proof for this theoretical hypothesis came from **9'''m**, an original 2.2.2 bicyclooctadiene isolated as co-product of **10m**. The latter was the result of a formal *para*-cycloaddition between distal double bond of allene and benzyl group in which the cinnamoyl alkene was untouched (scheme 54).



Scheme 54 experimental proof of allene activation

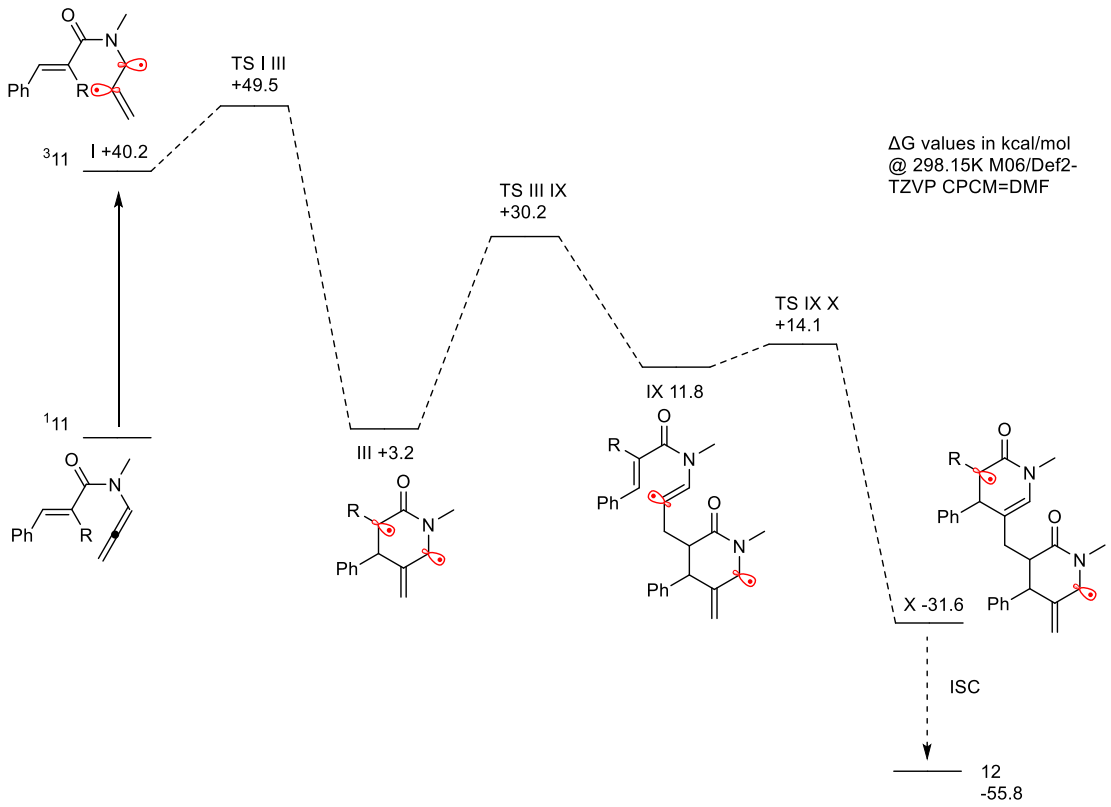
The activation of enallenamide gives ^{3}**9** (+41.4 Kcal/mol) that undergo 5-*exo-trig* cyclization affording the considerably more stable ^{3}**II** (ΔG = +7.5 kcal/mol). Intermolecular radical addition, which is usually wasteful in energetic terms due to the negative entropy, take place thanks to polarity reversal[111]. In detail, association of a second molecule of ^{1}**9** led to ^{3}**II**_1 (ΔG = +15.6 kcal/mol) that, through a barrier of 16.0 kcal/mol, convert to ^{3}**IV** (ΔG = +19.0 kcal/mol). The formation of a new C-C bond, which closed an additional 5-membered ring, delivered ^{3}**V** (ΔG = -19.9 kcal/mol). The two hydrogen atom transfers (HATs) that afforded the final cyclic acrylamide unit are unselective process, as shown by deuterium labelling experiments (***d*$_1$-9a** and ***d*$_1$-9m**). For this reason, the elaboration of a concise model for this pathway was not possible. However, based on the well-known 1,5 and 1,7 HATs[112–114], we modelled an alternative to get an idea of the energy involved. The first one might in principle occur via TS(**V**-1,7), which would require a barrier of +26.4 kcal/mol. The resulting triplet could then provide intermediate **VI** through a slightly lower barrier (+24.0 kcal/mol in ΔG). Both processes are energetically expensive. This remark, joined to the inconclusive result obtained from the deuterium labelling experiment above cited, fuels the hypothesis that more labile hydrogens present in the reaction mixture are involved.

Intermediate ^{3}**VI** is in the correct spatial arrangement to induce the attack of its allyl radical arm onto the aryl ring, providing the cyclohexadienyl radical fragment of ^{3}**VII** via **TS(VI-VII)** (ΔΔG = +4.7 kcal/mol). A reaction of aromatization driven by 1,5 HAT delivered ^{3}**VIII** (ΔG = -28.7 kcal/mol), as confirmed by deuterium labelling experiment. ISC close the cascade affording **10** with a largely negative Gibbs energy balance (ΔG = -75.5 kcal/mol). This pathway could explain the formation of biproduct **10'**. When the intramolecular *6-exo/endo-trig* cyclization occurs in the intermediate ^{3}**VI**, the radical addition may take place on both faces of the aryl ring. The absence of the correct geometry (**VII**$_{iso}$) forbit the key 1,5 HAT paving the way to a β-fragmentation that give aromatic **10'** and regenerate intermediate ^{3}**II** (Scheme 55).



Scheme 55 possible mechanistic rationale and DFT modelling results for the dimerization of 9.

Enallenamide ^{1}**11** is activated by eT in the same way of ^{1}**9**. Upon activation, the presence of the R group favours an unusual 6-*endo-trig* instead of a typically more convenient 5-*exo-trig* cyclization (ΔΔG = -1.6 kcal/mol). The result of this cyclization is intermediate ^{3}**III**. Similarly, to the above descripted route, the latter approaches an additional molecule of **11** and, when the α-acyl radical of ^{3}**III** adds to the sp^2 methylene of the second substrate molecule, intermediate ^{3}**IX** is delivered. The barrier for this dimerization is 21.3 Kcal/mol in ΔG. Another 6-*endo-trig* cyclization driven by the steric hindrance of the R group converts intermediate **IX** in **X** (ΔG = -31.6 kcal/mol). Finally, ISC followed by recombination of radicals affords **12 (**Scheme 56).



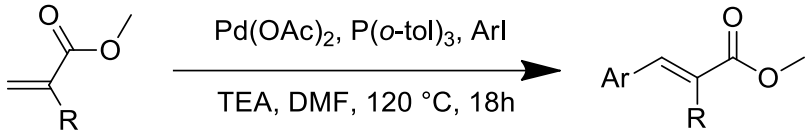
Scheme 56 possible mechanistic rationale and DFT modelling results for the dimerization of 11.

4.3 Conclusion

We described the first dimerization of allenamides. This method shows several interesting developments. Radical cascades herein reported are among the longest in literature, involving up to eleven elementary steps. Due to the molecular complexity obtained forming up to five new C-C bonds and the high number of stereocenters, both the yield and the diastereoselectivity are generally satisfactory. A broad range of functional groups are tolerated. The use of mild condition, cheap equipment and no special precaution, except for oxygen exclusion, make this protocol easily extendible. Last, but not least, the activation of allenamide cumulated double bond marks a starting point for future developments in the field of photocatalysis.

4.4 Experimental section

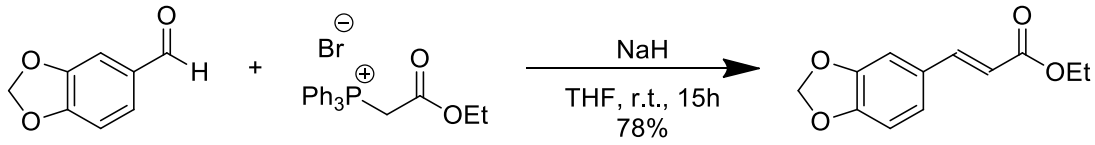
Representative procedure for the preparation of **9h, 9k, 11d, 11f** ester precursors



Precursor of	Ar	R	Yield
9h	4-OMe-C_6H_4	H	80%
9k	3-OMe-C_6H_4	H	99%
11d	4-Cl-C_6H_4	Me	27%
11f	4-*n*Bu-C_6H_4	Me	90%

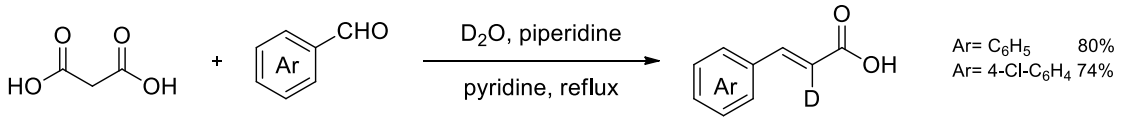
In a Schlenk tube equipped with a magnetic stirring bar under nitrogen atmosphere, were added $Pd(OAc)_2$ (0.02 equiv.), P(*o*-tol)$_3$ (0.04 equiv.), TEA (1.5 equiv.), acrylate (1.3 equiv.) and the aryl halide (1 equiv.) in DMF (1 M). The resulting mixture was stirred at 120 °C for 18 h. After complete conversion as monitored by TLC, the mixture was diluted with EtOAc, washed twice with water and a saturated LiCl solution, dried with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

Representative procedure for the preparation of **9l** ester precursor



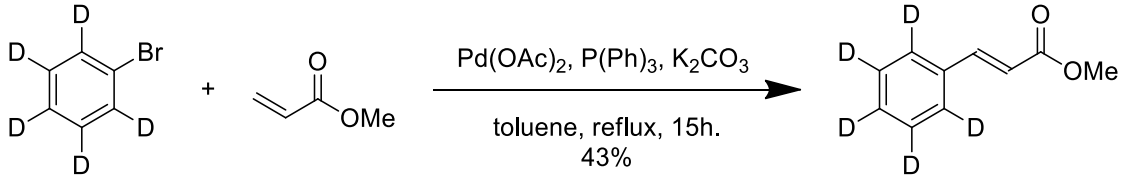
To a solution of triphenylphosphonium salt (1.15 equiv.) in THF (0.87 M) was added NaH (1.15 equiv., 60 % w in paraffin oil) at 0 °C and the resulting mixture was then stirred for 1 h. Then, benzo[d][1,3]dioxole-5-carbaldehyde (1 equiv.) was added and the reaction was mixed at room temperature overnight. After complete conversion as monitored by TLC, the solution was quenched with a saturated NH_4Cl solution, extracted with EtOAc (3 times) and washed with brine. The combined organic phase was finally dried over Na_2SO_4, concentrated under reduced pressure, and purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

Representative procedure for the preparation of α-deutero-trans-cinnamic acid.



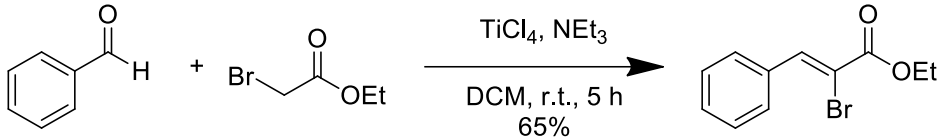
In a 25 mL round bottom flask equipped with magnetic stirring bar connected to a water-cooled-condenser a solution of malonic acid (1 equiv.), piperidine (0.35 equiv.) and D_2O (14 equiv.) in pyridine (1.5 M) were refluxed for 2 hours; the desired aryl aldehyde was then added and the mixture was stirred for additional 3 hours. The resulting mixture was poured in a HCl solution (10% m/V), the precipitate was filtered, washed with water and dried under vacuo affording the corresponding α-deutero-trans-cinnamic acid (deuterium incorporation: 88%).

Representative procedure for the preparation of (d_5)-methyl cinnamate



In a Schlenk equipped with a magnetic stirring bar were added bromobenzene-d_5 (1 equiv.), methyl acrylate (1.2 equiv.), K_2CO_3 (1.5 equiv.), $P(Ph)_3$ (0.04 equiv.), $Pd(OAc)_2$ (0.02 equiv.) in toluene (3.3 M) and the resulting mixture was refluxed overnight. After complete conversion as monitored by TLC, the reaction was filtered on celite, diluted with EtOAc and washed with water and brine. The combined organic layers were finally dried over Na_2SO_4, concentrated under reduced pressure, and purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

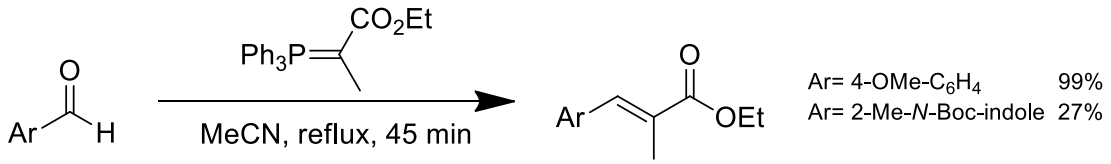
Representative procedure for the preparation of **11c** ester precursor[115]



In a three-necked round bottom flask were added freshly distilled benzaldehyde (1 equiv.) and 2-bromoethyl acetate (1.1 equiv.) in DCM (0.67 M). The mixture was stirred for 10 minutes and then $TiCl_4$ (1.2 equiv., 1 M solution in DCM) was added in drops over a

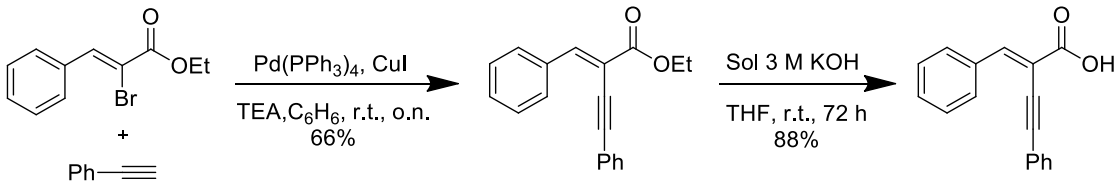
period of 10 minutes. The solution was stirred for 30 minutes at room temperature, then NEt_3 (2 equiv.) was added slowly, maintaining the temperature under 30 °C, and the resulting mixture was then stirred for 5 h. After complete conversion as monitored by TLC, the solution was diluted with DCM and washed with a 1 M HCl solution, water and brine. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure and the resulting crude was purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

Representative procedure for the preparation of **11e**, **11g** ester precursors



To a solution of phosphonium ylide in MeCN (0.12 M) the desired aryl aldehyde was added. The resulting mixture was refluxed 45 min under stirring. After complete conversion of reagents, the mixture was concentrated under reduced pressure and purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

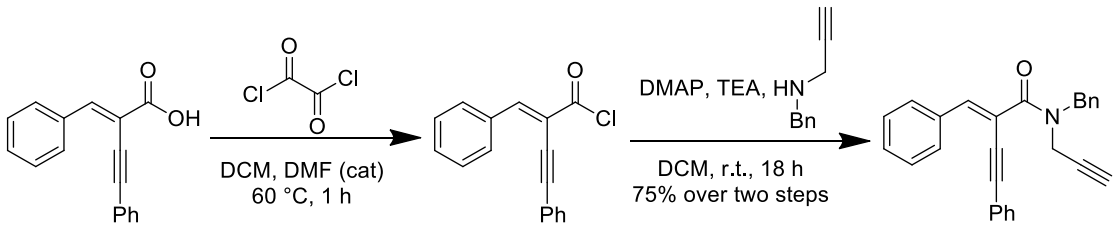
Preparation of enyne **11c** precursor



In a Schlenk equipped with a magnetic stirring bar were added (Z)-ethyl 2-bromo-3-phenylacrylate (1 equiv.), ethynylbenzene (1.2 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), CuI (0.1 equiv.), TEA (2 equiv.) in benzene (0.3 M) and the solution was stirred at room temperature overnight. After complete conversion as monitored by TLC, the mixture was filtered on celite and concentrated under reduced pressure. The crude was then purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

To a solution of (E)-ethyl 2-benzylidene-4-phenylbut-3-ynoate (1 equiv.) in THF (0.27 M) was added a 3 M solution of KOH (10 equiv.). The biphasic mixture was vigorously stirred at room temperature for 72 h. After complete conversion as monitored by TLC, the mixture was concentrated under reduced pressure and acidified to pH = 1 with a 1 M

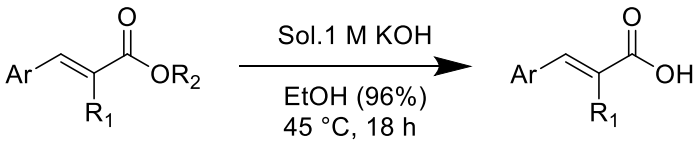
HCl solution; during the process, the formation of a precipitate was observed. The solid was filtered, washed with water, and dried under high vacuum to afford (E)-2-benzylidene-4-phenylbut-3-ynoic acid.



In a 25 mL round bottom flask equipped with a magnetic stirring bar were added (E)-2-benzylidene-4-phenylbut-3-ynoic acid (1 equiv.), oxalyl chloride (1.5 equiv.), DMF (3 drops) in DCM (0.6 M) and the solution was stirred at 60 °C for 1 h. The mixture was then concentrated under reduced pressure to afford the desired acyl chloride.

To a solution of secondary amine (1 equiv.), TEA (1 equiv.), DMAP (0.02 equiv.) in DCM (0.25 M) was added acyl chloride (1 equiv.) at 0 °C, and the solution was then stirred at room temperature for 18 h. After complete conversion as monitored by TLC, the solution was diluted with DCM and washed with a saturated NH_4Cl solution followed by a saturated $NaHCO_3$ one. The aqueous layers were extracted with DCM (3 times), and the combined organic phase was finally washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure; the crude was purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

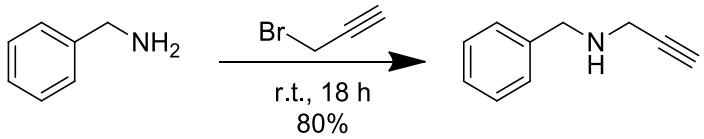
Representative procedure for the preparation of cinnamic acids from the corresponding esters.



Precursor of	Ar	R^1	R^2	Yield
***d*$_5$-9a**	C_6D_5	H	Me	50%
9k	4-OMe-C_6H_4	H	Me	88%
9l	3,4-methylendioxy-C_6H_3	H	Et	95%
11b	C_6H_5	*n*Pr	Et	85%
11d	4-Cl-C_6H_4	Me	Me	99%
11e	4-OMe-C_6H_4	Me	Me	86%
11f	4-*n*Bu-C_6H_4	Me	Me	68%
11g	2-Me-N-Boc-indole	Me	Et	81%

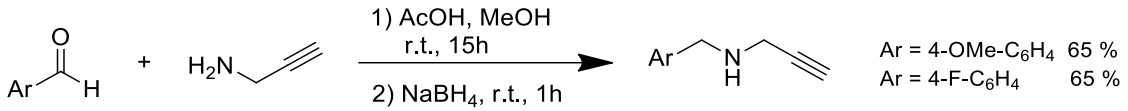
In a round bottom flask equipped with a stir bar were added the desired ester (1 equiv.), EtOH (0.15 M) and a 1 M solution of KOH (2.5 equiv.). The resulting mixture was stirred 18 h at 45 °C. After complete conversion as monitored by TLC, the mixture was concentrated under reduced pressure and acidified to pH = 1 with a 1 M HCl solution. During the process, the formation of a precipitate was observed. The solid was filtered, washed with water and dried under high vacuum to afford the corresponding cinnamic acid.

Representative procedure for the preparation of benzyl propargylamine



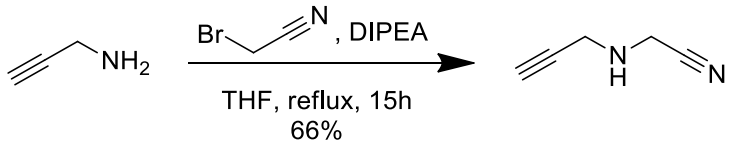
In a round bottom flask equipped with a magnetic stirring bar, propargyl bromide (1 equiv., 80% w in toluene) was added at 0 °C to benzylamine (6 equiv.) and the resulting solution was stirred overnight at room temperature. After complete conversion as monitored by TLC, the mixture was quenched with a saturated $NaHCO_3$ solution and extracted with Et_2O (3 times). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was finally purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

Representative procedure for the preparation of substituted benzyl propargylamine



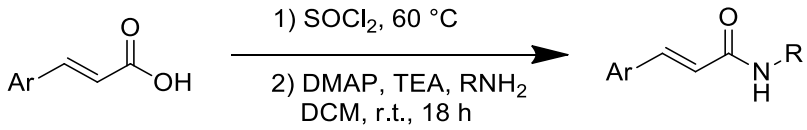
To a solution of propargyl amine (1 equiv.) and aryl aldehyde (1.08 equiv.) in MeOH (0.6 M) was added AcOH (1 drop). The resulting mixture was then stirred overnight at room temperature. $NaBH_4$ (1.5 equiv.) was added at 0 °C and the solution was then stirred for 1 h prior to the evaporation of the solvent. The mixture was diluted with water, extracted with DCM (2 times), and the combined organic layers were then washed with a 1 M HCl solution. Aqueous layers were neutralized, extracted with DCM (2 times), and the resulting organic phase was finally washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by chromatography on silica gel (DCM/EtOAc gradient).

Representative procedure for the preparation of 2-(prop-2-yn-1-ylamino)acetonitrile.



In a 25 mL round bottom flask equipped with a magnetic stirring bar were added propargyl amine (1 equiv.), 2-bromoacetonitrile (1.2 equiv.), DIPEA (1.2 equiv.) in THF (0.33 M) and the resulting mixture was refluxed overnight. After complete conversion as monitored by TLC, the reaction was diluted with EtOAc and washed with brine. The combined organic phase was dried over Na_2SO_4, concentrated under reduced pressure, and purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

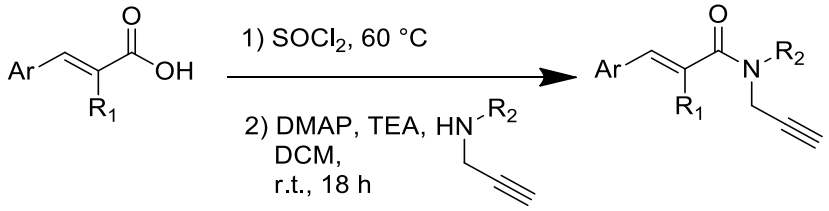
Representative procedure for preparation of cinnamamide precursors



Precursor of	Ar	R^1	R^2	Yield
***d*$_1$-9a**	C_6H_5	D	Bn	92 %
9b	C_6H_5	H	C_9H_{19}	96 %
9e	C_6H_5	H	C_3H_5	94 %
9g	4-Br-C_6H_4	H	Bn	70 %
9i	2-Me-C_6H_4	H	Bn	77 %
11k	C_6H_5	Me	C_3H_5	87 %

In a 25 mL round bottom flask equipped with a magnetic stirring bar, the desired acid was dissolved in $SOCl_2$ (1.67 M) and a catalytic amount of DMF (3 drops) was added. The solution was stirred for 1 h at 60 °C. Then, the mixture was concentrated under reduced pressure to afford the acyl chloride, that was added to a solution of DMAP (0.02 equiv.), TEA (1 equiv.) and primary amine (1 equiv.) in DCM (0.25 M) at 0 °C. The mixture was stirred for 18 h at room temperature. After complete conversion as monitored by TLC, the solution was diluted with DCM and washed with a saturated NH_4Cl solution followed by a saturated $NaHCO_3$ one. The aqueous layers were extracted with DCM (3 times), and the combined organic phase was finally washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and the crude was purified by chromatography on silica gel (*n*-hexane/EtOAc gradient). Cinnamamide precursors of **9b, 9d, 9e** were directly prepared from commercially available cinnamoyl chloride.

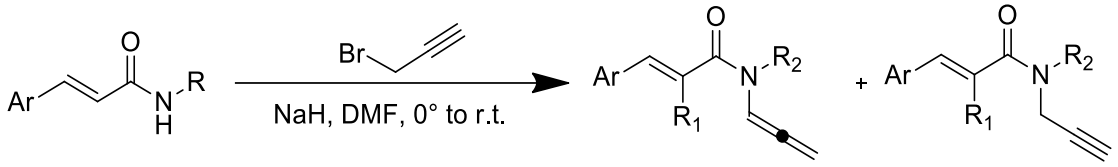
Representative procedure for the preparation of 1,6-enynes



Precursor of	Ar	R^1	R^2	Yield
9a	C_6H_5	H	Bn	71 %
***d*$_5$-9a**	C_6D_5	H	Bn	60 %
9c	C_6H_5	H	CH_2Bn	74 %
9f	4-Cl-C_6H_4	H	CH_2Bn	76 %
9h	4-OMe-C_6H_4	H	Bn	80 %
9j	3-Me-C_6H_4	H	Bn	79 %
9k	3-OMe-C_6H_4	H	Bn	61 %
9l	3,4-methylendioxy-C_6H_3	H	Bn	70 %
9m	4-Cl-C_6H_4	D	Bn	58%
11b	C_6H_5	*n*Pr	Bn	65 %
11d	4-Cl-C_6H_4	Me	Bn	51 %
11e	4-OMe-C_6H_4	Me	Bn	54 %
11f	4-*n*Bu-C_6H_4	Me	Bn	53 %
11g*	2-Me-N-Boc-indole	Me	Bn	55 %
11h	C_6H_5	Me	PMB	68 %
11i	C_6H_5	Me	CH_2-4-F-C_6H_4	78 %
11j	C_6H_5	Me	CH_2CN	72 %

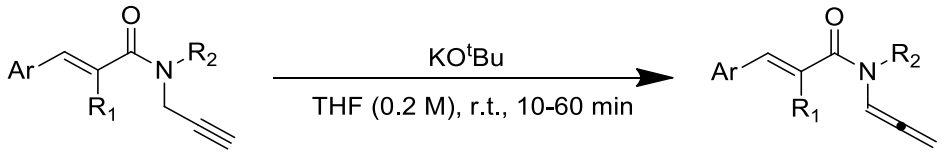
In a 25 mL round bottom flask equipped with a magnetic stirring bar, the desired acid was dissolved in $SOCl_2$ (1.67 M) and a catalytic amount of DMF (3 drops) was added. The solution was stirred for 1 h at 60 °C. Then, the mixture was concentrated under reduced pressure to afford the acyl chloride, that was added to a solution of DMAP (0.02 equiv.), TEA (1 equiv.) and secondary amine (1 equiv.) in DCM (0.25 M) at 0 °C. The mixture was stirred for 18 h at room temperature. After complete conversion as monitored by TLC, the solution was diluted with DCM and washed with a saturated NH_4Cl solution followed by a saturated $NaHCO_3$ one. The aqueous layers were extracted with DCM (3 times), and the combined organic phase was finally washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and the crude was purified by chromatography on silica gel (*n*-hexane/EtOAc gradient). Enyne precursors of **9a, 9c** were directly prepared from commercially available cinnamoyl chloride. Acyl chloride precursor of **11g** was prepared using a solution of oxalyl chloride (1.5 equiv.) in DCM (0.6 M) instead of $SOCl_2$.

Synthesis of 1-6 enallenes [GP-1a]:



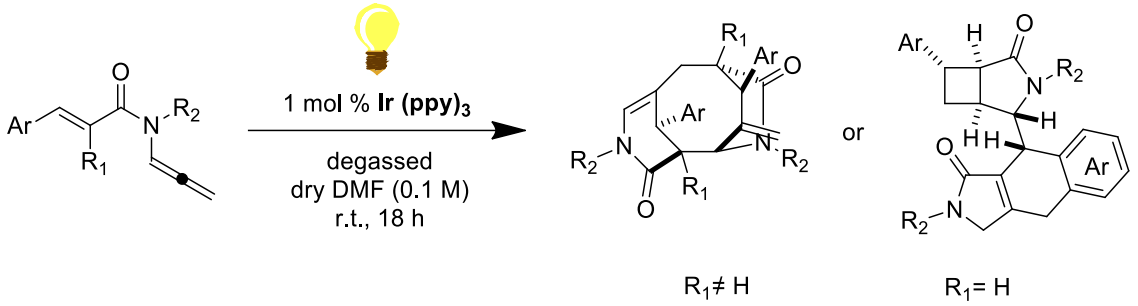
To a solution of acrylamide (1 equiv.) in DMF at 0° C NaH (60% in paraffine oil, 1.3 equiv.) was slowly added and the mixture was stirred 1h. Then a solution of propargyl bromide (80% in toluene, 1.5 equiv.) was slowly added and the reaction was stirred at r.t.. After complete conversion monitoring by TLC, the mixture was quenched with a saturated NH_4Cl solution and extracted with EtOAc (3 times). The combined organic layers were washed with a saturated LiCl solution (3 times), dried over over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (*n*-hexane/EtOAc gradient) affording the corresponding products **9**.

Synthesis of 1-6 enallenes [GP-1b]:



The desired enyne (1 equiv.) and THF (0.20 M) were sequentially added to a Schlenk tube equipped with a magnetic stirring bar. The resulting mixture was stirred at room temperature for 10 minutes prior to the addition of *t*BuOK (0.2 equiv.). After complete conversion as monitored by TLC, a saturated NH_4Cl solution (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 solution was concentrated under reduced pressure and the crude purified by chromatography on silica gel (*n*-hexane/EtOAc gradient).

Photocatalytic reactions [GP-2]:



To a vial charged with substrate **7** or **9** (1 equiv., 0.15-0.3 mmol) and **Ir(ppy)$_3$** (1 mol%), dry and degassed DMF (0.1 M) was added through a syringe. The solution was transferred in two NMR tubes capped with a rubber septum and it was then degassed through three freeze-pump cycles. The homogeneous solution was placed in an oil bath kept at 25 °C and irradiated with LED stripes for 18 hours indicatively. Conversion was monitored by TLC and the mixture was then concentrated in vacuo. The residue was purified by chromatography on silica gel; the catalyst was removed using toluene as eluent prior to the separation of desired products (*n*-hexane/EtOAc, under gradient).

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N-benzyl-N-(propa-1,2-dien-1-yl)cinnamamide. 9a was prepared following general procedure **GP-1b** from the corresponding enyne (275 mg, 1.0 mmol). Yellow solid (132.7 mg, 48% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, Acetone d_6) δ 7.81 – 7.70 (m, 3H RotA, 2H RotB), 7.65 – 7.59 (m, 1H RotA, 1H RotB), 7.48 – 7.24 (m, 9H RotA, 9H RotB), 7.17 (d, J = 15.3 Hz, 1H RotB), 5.38 (d, J = 6.3 Hz, 2H RotA, 2H RotB), 4.99 (s, 2H RotB), 4.84 (s, 2H rotA). **^{13}C NMR** (101 MHz, Acetone) δ 202.7 (Cq, RotB), 202.1 (Cq, RotA), 164.2 (Cq, RotA), 164.1 (Cq, RotB), 143.8 (CH, RotB), 143.4 (CH, RotA), 138.21 (Cq, RotA), 138.18 (Cq, RotB), 135.3 (Cq, RotA), 135.2 (Cq, RotB), 129.9, 128.8, 128.7, 128.2, 128.1, 127.7, 127.2, 126.9, 126.3, 117.4 (CH, RotB), 117.2 (CH, RotA), 100.4 (CH, RotA), 99.5 (CH, RotB), 87.0 (CH_2, RotB), 86.0 (CH_2, RotA), 48.4 (CH_2, RotB), 47.3 (CH_2, RotA). **ESI-MS** calcd for $C_{19}H_{18}NO$ $[M+H]^+$ 276.14, found 276.16.

(*E*)-N-benzyl-3-(2,3,4,5,6-pentadeuterophenyl)-N-(propa-1,2-dien-1-yl)acrylamide. *d*$_5$-9a was prepared following general procedure **GP-1b** from the corresponding enyne (218 mg, 0.78 mmol). Yellow solid (119.8 mg, 55% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (apparent dd, J = 10.6, 4.5 Hz, 1H RotA, 2H RotB), 7.41 – 7.20 (m, 5H RotA, 5H RotB), 7.00 (d, J = 15.4 Hz, 1H RotA), 6.91 (t, J = 5.6 Hz, 1H RotA), 6.78 (d, J = 15.8 Hz, 1H RotB), 5.33 (d, J = 6.4 Hz, 2H RotA, 2H RotB), 4.83 (s, 2H RotA, 2H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 202.4, 165.0, 144.6, 143.9, 137.6, 137.2, 134.8, 128.9, 128.8, 128.4, 128.1, 127.5, 127.1, 126.1, 116.9, 100.2, 100.0, 87.7, 86.8, 49.3, 48.2. **ESI-MS** calcd for $C_{19}H_{13}D_5NO$ $[M+H]^+$ 281.17, found 281.28.

(*E*)-N-benzyl-2-deutero-3-phenyl-N-(propa-1,2-dien-1-yl)acrylamide *d*$_1$-9a was prepared following general procedure **GP-1b** from the corresponding enyne (354.0 mg, 1.34 mmol). Dark orange solid (188.6 mg, 53% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 1H RotA, 1H RotB), 7.63 – 7.18 (m, 8H), 7.03 (d, J = 15.4 Hz, 0.12H RotA), 6.93 (brs, 1H RotA), 6.81 (d, J = 15.4 Hz, 0.12H RotB), 5.36 (d, J = 6.0 Hz, 2H RotA, 2H RotB), 4.89 – 4.82 (m, 2H RotA, 2H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 202.4, 165.0, 144.6, 143.9, 137.6, 137.2, 134.9, 130.0, 128.9, 128.8, 128.4, 128.0, 127.5, 127.2, 126.1, 116.9, 116.6

(t, J = 24.0 Hz, CD), 100.2, 100.0, 87.7, 86.8, 49.3, 48.2. **ESI-MS** calcd for $C_{19}H_{17}D_1NO$ $[M+H]^+$ 277.15, found 277.40.

N-nonyl-N-(propa-1,2-dien-1-yl)cinnamamide. 9b was directly prepared following general procedure **GP-1a** from the corresponding cinnamamide (1.0 g, 3.65 mmol). Brown oil (306 mg, 31% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, J = 15.3 Hz, 1H RotB), 7.71 – 7.60 (m, 2H RotA), 7.54 (dd, J = 7.4, 2.0 Hz, 2H RotA, 2H RotB), 7.38 (brs, 2H RotA, 3H RotB), 7.05 – 6.79 (m, 3H RotA, 2H RotB), 5.47 – 5.32 (m, 2H), 3.69 – 3.41 (m, 2H), 1.73 – 1.53 (m, 2H), 1.45 – 1.15 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.6 (Cq), 201.9 (Cq), 164.8 (CH), 164.3 (CH), 144.2 (CH), 143.2 (CH), 135.2 (CH), 129.9 (Cq), 129.8 (Cq), 128.9 (CH), 127.9 (CH), 117.3 (CH), 116.7 (CH), 100.3 (CH), 99.2 (CH), 86.8 (CH_2), 86.1 (CH_2), 45.9 (CH_2), 45.0 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3). **ESI-MS** calcd for $C_{21}H_{30}NO$ $[M+H]^+$ 312.23, found 312.28.

N-phenethyl-N-(propa-1,2-dien-1-yl)cinnamamide 9c was prepared following general procedure **GP-1b** from the corresponding enyne (200 mg, 0.69 mmol). Colourless viscous oil (81.3 mg, 40% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.63 (m, 1H RotA, 2H RotB), 7.60 – 7.51 (m, 1H RotA, 1H RotB), 7.46 – 7.21 (m, 9H RotA, 9H RotB), 7.03 – 6.85 (m, 2H RotA), 6.60 (d, J = 15.3 Hz, 1H RotB), 5.51 (d, J = 6.5 Hz, 2H RotB), 5.44 (d, J = 5.9 Hz, 2H RotA), 3.83 (t, J = 7.0 Hz, 2H RotA, 2H RotB), 3.06 – 2.85 (m, 2H RotA, 2H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.6 (Cq, RotB), 201.8 (Cq, RotA), 164.7 (Cq, RotA), 164.5 (Cq, RotB), 144.0 (Cq, RotB), 143.5 (Cq, RotA), 138.4 (Cq, RotA), 135.1 (Cq, RotB), 129.9, 128.9, 128.8, 128.5, 127.9, 126.9, 126.4, 117.0 (CH, RotA), 116.6 (CH, RotB), 100.3 (CH, RotA), 98.9 (CH, RotB), 87.1 (CH_2, RotB), 86.5 (CH_2, RotA), 47.6 (CH_2, RotB), 46.7 (CH_2, RotA), 35.0 (CH_2, RotB), 33.7 (CH_2, RotA). **ESI-MS** calcd for $C_{20}H_{19}NNaO$ $[M+Na]^+$ 312.14, found 312.06.

N-phenyl-N-(propa-1,2-dien-1-yl)cinnamamide. 9d was prepared following general procedure **GP-1a** from the corresponding cinnamamide (350 mg, 1.34 mmol). Yellow oil

(299 mg, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (t, *J* = 6.3 Hz, 1H), 7.73 (d, *J* = 15.5 Hz, 1H), 7.49 – 7.39 (m, 3H), 7.29 (s, 5H), 7.27 – 7.22 (m, 2H), 6.27 (d, *J* = 15.5 Hz, 1H), 5.05 (d, *J* = 6.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.2 (Cq), 163.9 (Cq), 143.2 (CH), 139.1 (Cq), 134.9 (Cq), 129.9 (CH), 129.4 (2CH), 128.9 (2CH), 128.7 (2CH), 128.6 (CH), 128.0 (2CH), 118.0 (CH), 101.4 (CH), 86.5 (CH_2). **ESI-MS** calcd for $C_{18}H_{15}NNaO$ $[M+Na]^+$ 284.10, found 284.14.

N-cyclopropyl-N-(propa-1,2-dien-1-yl)cinnamamide. 9e was prepared following general procedure **GP-1a** from the corresponding cinnamamide (225.3 mg, 1.0 mmol). Yellow liquid (127 mg, 56% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 15.6 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.49 – 7.27 (m, 4H), 5.36 (d, *J* = 6.5 Hz, 1H), 2.76 (tt, *J* = 6.9, 3.9 Hz, 1H), 1.02 (q, *J* = 7.1 Hz, 1H), 0.91 – 0.81 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.6 (Cq), 166.2 (Cq), 143.2 (CH), 135.3 (Cq), 129.9 (CH), 128.9 (CH), 128.0 (CH), 118.3 (CH), 99.6 (CH), 85.5 (CH_2), 28.1 (CH), 10.1 ($2CH_2$). **ESI-MS** calcd for $C_{15}H_{16}NO$ $[M+H]^+$ 226.29, found 226.24.

(*E*)-3-(4-chlorophenyl)-N-phenethyl-N-(propa-1,2-dien-1-yl)acrylamide 9f was prepared following general procedure **GP-1b** from the corresponding enyne (489.1 mg, 1.49 mmol). Orange oil (305 mg, 63% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.8 – 7.0 (m, 4H RotA, 5H RotB), 6.9 – 6.8 (m, 2H RotA), 6.5 (d, *J* = 15.3 Hz, 1H RotB), 5.49 (d, *J* = 6.2 Hz, 2H RotA), 5.41 (d, *J* = 6.2 Hz, 2H RotB), 3.9 – 3.7 (m, 2H RotA, 2H RotB), 3.0 – 2.9 (m, 3H RotA, 3H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.6, 201.8, 164.4, 164.3, 162.4, 145.6, 142.4, 142.1, 139.0, 138.4, 138.1, 135.7, 133.6, 129.5, 129.4, 129.1, 129.0, 129.0, 128.9, 128.8, 128.7, 128.5, 126.9, 126.8, 126.4, 117.6, 117.2, 100.2, 98.8, 87.2, 86.6, 47.6, 46.8, 35.0, 33.7. **ESI-MS** calcd for $C_{20}H_{19}ClNO$ $[M+H]^+$ 324.11, found 324.21.

(*E*)-N-benzyl-3-(4-bromophenyl)-N-(propa-1,2-dien-1-yl)acrylamide. 9g was directly prepared following general procedure **GP-1a** from the corresponding cinnamamide (700 mg, 2.79 mmol). White solid (263 mg, 37% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (t, *J* = 6.3 Hz, 1H RotB), 7.72 (d, *J* = 15.3 Hz, 1H RotA, 1H RotB), 7.58 – 7.24 (m, 9H RotA, 9H RotB), 7.02 (d, *J* =

15.4 Hz, 1H RotA), 6.89 (t, *J* = 6.0 Hz, 1H RotA), 6.77 (d, *J* = 15.3 Hz, 1H RotB), 5.36 (d, *J* = 6.4 Hz, 2H RotA, 2H RotB), 4.84 (d, *J* = 6.5 Hz, 2H RotA, 2H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.6 (Cq, RotB), 202.5 (Cq, RotA), 164.8 (Cq, RotA), 164.7 (Cq, RotB), 143.2 (CH, RotB), 142.6 (CH, RotA), 137.4 (Cq, RotA), 137.1 (Cq, RotB), 132.1, 129.4, 128.9, 127.6, 126.0, 124.2 (Cq RotA, Cq RotB), 117.6, 100.1, 100.0, 87.8, 86.9, 49.3, 48.3. **ESI-MS** calcd for $C_{19}H_{17}BrNO$ $[M+H]^+$ 354.05, found 354.06.

(*E*)-N-benzyl-3-(4-methoxyphenyl)-N-(propa-1,2-dien-1-yl)acrylamide. 9h was prepared following general procedure **GP-1b** from the corresponding enyne (289 mg, 0.94 mmol). White solid (245 mg, 85% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.70 (m, 2H RotA, 1H RotB), 7.57 – 7.22 (m, 7H RotA, 7H RotB), 6.98 – 6.82 (m, 3H RotA, 3H RotB), 6.67 (d, *J* = 16.0 Hz, 1H RotB), 5.35 (d, *J* = 6.3 Hz, 2H RotA, 2H RotB), 4.84 (s, 2H RotA, 2H RotB), 3.92 – 3.79 (m, 3H RotA, 3H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 202.4, 165.4, 165.3, 161.2, 144.4, 143.7, 137.7, 137.3, 129.6, 128.9, 128.3, 128.1, 127.7, 127.4, 126.1, 114.4, 114.3, 100.3, 100.1, 87.6, 86.7, 55.4, 49.2, 48.2. **ESI-MS** calcd for $C_{20}H_{20}NO_2$ $[M+H]^+$ 306.38, found 306.24.

(*E*)-N-benzyl-N-(propa-1,2-dien-1-yl)-3-(o-tolyl)acrylamide. 9i was prepared following general procedure **GP-1a** from the corresponding cinnamamide (700.0 mg, 2.79 mmol). Orange solid (530.0 mg, 65% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 15.3 Hz, 1H RotA, 1H RotB), 7.80 (t, *J* = 6.3 Hz, 1H RotB), 7.57 (d, *J* = 7.1 Hz, 1H RotA), 7.39 – 7.08 (m, 7H RotA, 8H RotB), 6.95 – 6.87 (m, 2H RotA), 6.68 (d, *J* = 15.1 Hz, 1H RotB), 5.34 (d, *J* = 6.4 Hz, 2H RotA, 2H RotB), 4.82 (s, 2H RotA, 2H RotB), 2.45 (s, 3H RotA), 2.40 (s, 3H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 202.4, 165.0, 142.4, 141.8, 137.7, 137.2, 134.1, 130.8, 129.7, 128.9, 128.4, 128.1, 127.5, 126.4, 126.3, 126.2, 126.2, 126.1, 118.2, 100.0, 87.7, 86.8, 49.3, 48.3, 19.9. **ESI-MS** calcd for $C_{20}H_{20}NO$ $[M+H]^+$ 290.15, found 290.26.

(*E*)-N-benzyl-N-(propa-1,2-dien-1-yl)-3-(m-tolyl)acrylamide. 9j was prepared following general procedure **GP-1b** from the corresponding enyne (261.3 mg, 0.90

mmol). White solid (187.0 mg, 71% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.73 (m, 1H RotA, 2H RotB), 7.45 – 7.13 (m, 9H RotA, 9H RotB), 7.07 – 6.91 (m, 2H RotA), 6.80 (d, *J* = 15.3 Hz, 1H RotB), 5.35 (d, *J* = 6.2 Hz, 2H RotA, 2H RotB), 4.85 (s, 2H RotA, 2H RotB), 2.38 (d, *J* = 18.9 Hz, 3H RotA, 3H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 202.4, 165.2, 165.1, 144.9, 144.2, 138.5, 137.6, 137.2, 135.0, 134.9, 130.8, 128.9, 128.7, 128.6, 128.4, 128.0, 127.5, 127.1, 126.1, 125.2, 125.1, 116.6, 100.3, 100.0, 87.7, 86.8, 49.3, 48.2, 21.3. **ESI-MS** calcd for $C_{20}H_{20}NO$ $[M+H]^+$ 290.15, found 290.26.

(*E*)-N-benzyl-3-(3-methoxyphenyl)-N-(propa-1,2-dien-1-yl)acrylamide. 9k was prepared following general procedure **GP-1b** from the corresponding enyne (298 mg, 0.98 mmol). Yellow solid (131.0 mg, 44% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.69 (m, 2H RotA, 1H RotB), 7.39 – 7.20 (m, 5H RotA, 5H RotB), 7.15 (d, *J* = 7.4 Hz, 1H RotA), 7.10 – 6.85 (m, 3H RotA, 4H RotB), 6.76 (d, *J* = 15.4 Hz, 1H RotB), 5.34 (d, *J* = 6.4 Hz, 2H RotA, 2H RotB), 4.86 – 4.79 (m, 2H RotA, 2H RotB), 3.84 (s, 3H RotA), 3.79 (s, 3H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 202.4, 165.1, 164.9, 159.9, 159.8, 144.5, 143.9, 137.5, 137.2, 136.4, 136.3, 129.8, 128.9, 128.4, 128.1, 127.5, 127.2, 126.1, 120.6, 117.3, 117.3, 115.6, 113.2, 100.2, 100.0, 87.7, 86.8, 55.3, 53.4, 49.3, 48.2. **ESI-MS** calcd for $C_{20}H_{20}NO_2$ $[M+H]^+$ 306.15, found 306.24.

(*E*)-3-(benzo[d][1,3]dioxol-5-yl)-N-benzyl-N-(propa-1,2-dien-1-yl)acrylamide 9l was prepared following general procedure **GP-1b** from the corresponding enyne (250.0 mg, 0.78 mmol). White solid (154 mg, 62% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (t, *J* = 6.2 Hz, 1H RotB), 7.71 (d, *J* = 15.2 Hz, 1H RotA, 1H RotB), 7.45 – 7.19 (m, 5H RotA, 5H RotB), 7.13 – 6.76 (m, 5H RotA, 3H RotB), 6.62 (d, *J* = 15.2 Hz, 1H RotB), 6.03 (s, 2H RotA), 6.00 (s, 2H RotB), 5.37 – 5.33 (m, 2H RotA, 2H RotB), 4.83 (brs, 2H RotA, 2H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 202.4, 165.2, 165.1, 149.4, 148.3, 148.2, 144.4, 143.8, 137.5, 137.2, 129.4, 128.9, 128.4, 128.0, 127.5, 127.1, 126.1, 124.4, 124.2, 114.8, 108.6, 106.4, 101.5, 100.2, 100.1, 87.6, 86.7, 49.2, 48.2. **ESI-MS** calcd for $C_{20}H_{18}NO_3$ $[M+H]^+$ 320.13, found 320.22.

(*E*)-N-benzyl-2-deutero-3-(4-chlorophenyl)-N-(propa-1,2-dien-1-yl)acrylamide. 9m was prepared following general procedure **GP-1b** from the corresponding enyne (248.1 mg, 0.8 mmol). White solid (126.0 mg, 51% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.8 (t, *J* = 6.3 Hz, 1H RotB), 7.8 – 7.7 (m, 1H RotA, 1H RotB), 7.5 – 7.2 (m, 9H RotA, 9H RotB), 7.0 (d, *J* = 15.0 Hz, 0.20H RotA), 6.9 (t, *J* = 5.8 Hz, 1H RotA), 6.8 (d, *J* = 15.3 Hz, 0.20H RotB), 5.4 (d, *J* = 6.3 Hz, 2H RotA, 2H RotB), 4.8 (d, *J* = 6.8 Hz, 2H RotA, 2H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 165.3, 164.7, 143.1, 142.5, 140.1, 137.1, 135.8, 133.4, 129.4, 129.18, 129.11, 129.0, 128.9, 128.8, 128.4, 128.0, 128.0, 127.7, 127.6, 127.2, 126.0, 117.5, 100.0, 87.8, 86.8, 49.3, 48.3. **ESI-MS** calcd for $C_{19}H_{16}DClNO$ $[M+H]^+$ 311.11, found 311.48. (*Slow decomposition during the measurement of the NMR sample was observed*).

(*E*)-N-benzyl-2-methyl-3-phenyl-N-(propa-1,2-dien-1-yl)acrylamide. 11a was prepared following general procedure **GP-1b** from the corresponding enyne (587.0 mg, 2.03 mmol). White solid (475 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 6.96 (m, 12H), 6.69 (s, 1H), 5.32 (d, *J* = 6.2 Hz, 2H), 4.83 (s, 2H), 2.38 – 2.06 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.2, 171.1, 137.6, 135.6, 132.1, 129.1, 128.5, 128.4, 127.7, 127.2, 101.5, 87.3, 47.3, 16.1. **ESI-MS** calcd for $C_{20}H_{20}NO$ $[M+H]^+$ 290.15, found 290.20.

(*E*)-N-benzyl-2-benzylidene-N-(propa-1,2-dien-1-yl)pentanamide. 11b was prepared following general procedure **GP-1b** from the corresponding enyne (587.0 mg, 1.85 mmol). Viscous oil (354.8 mg, 60% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.06 (m, 10H), 6.64 (brs, 1H), 5.30 (brs, 2H), 4.82 (s, 2H), 2.58 (brs, 2H), 1.64 – 1.46 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.5 (Cq), 171.2 (Cq), 137.6 (Cq), 137.3 (CH), 135.7 (Cq), 131.7 (Cq), 128.9 (2CH), 128.4 (4CH), 127.9 (2CH), 127.7 (CH), 127.1 (CH), 102.0 (CH), 87.3 (CH_2), 47.1 (CH_2), 31.7 (CH_2), 21.6 (CH_2), 14.2 (CH_3). **ESI-MS** calcd for $C_{22}H_{24}NO$ $[M+H]^+$ 318.18, found 318.26.

(*E*)-N-benzyl-2-benzylidene-4-phenyl-N-(propa-1,2-dien-1-yl)but-3-ynamide. 11c was prepared following general procedure **GP-1b** from the corresponding enyne (389.0

mg, 0.85 mmol). Red viscous oil (121.3 mg, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 – 7.77 (m, 2H), 7.64 – 7.00 (m, 15H), 5.45 – 5.20 (m, 2H), 5.15 – 4.80 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.6, 200.8, 166.4, 163.7, 143.9, 141.6, 137.3, 135.0, 131.5, 129.9, 129.5, 129.0, 128.5, 128.4, 128.4, 127.7, 127.1, 126.5, 122.7, 118.5, 116.7, 102.6, 100.3, 99.2, 87.6, 87.3, 85.2, 53.4, 47.9, 47.0. **ESI-MS** calcd for $C_{27}H_{22}NO$ $[M+H]^+$ 376.17, found 376.29.

(*E*)-N-benzyl-3-(4-chlorophenyl)-2-methyl-N-(propa-1,2-dien-1-yl)acrylamide. 11d was prepared following general procedure **GP-1b** from the corresponding enyne (389.0 mg, 0.85 mmol). Red viscous oil (121.3 mg, 60% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 9H RotA, 10H RotB), 6.7 (t, J = 6.3 Hz, 1H RotA), 6.6 (brs, 1H RotA, 1H RotB), 5.4 – 5.3 (m, 2H RotA, 2H RotB), 4.8 (s, 2H RotA, 2H RotB), 2.2 – 2.0 (m, 3H RotA, 3H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.9, 200.8, 170.6, 169.9, 137.5, 136.5, 134.0, 133.9, 132.8, 132.7, 130.4, 129.0, 129.0, 128.9, 128.6, 128.6, 128.5, 128.4, 128.3, 127.9, 127.3, 127.2, 126.4, 100.5, 98.3, 87.5, 87.5, 49.9, 46.4, 22.1, 16.2. **ESI-MS** calcd for $C_{20}H_{19}ClNO$ $[M+H]^+$ 324.11, found 324.04.

(*E*)-N-benzyl-3-(4-methoxyphenyl)-2-methyl-N-(propa-1,2-dien-1-yl)acrylamide. 11e was prepared following general procedure **GP-1b** from the corresponding enyne (434.4 mg, 1.36 mmol). Colourless viscous oil (334.6 mg, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 8H), 6.95 – 6.85 (m, 2H), 6.62 (brs, 1H), 5.32 – 5.25 (m, 2H), 4.80 (s, 2H), 3.82 (s, 3H), 2.13 (brs, 3H). **^{13}C NMR** (400 MHz, $CDCl_3$) δ 200.9 (Cq), 172.2 (Cq), 159.2 (Cq), 137.7 (CH), 131.8 (Cq), 130.6 (2CH), 130.0 (Cq), 128.5 (2CH), 128.3 (Cq), 127.6 (2CH), 127.1 (CH), 113.8 (2CH), 101.5 (CH), 87.3 (CH_2), 55.3 (CH_3), 47.7 (CH_2), 16.2 (CH_3). **ESI-MS** calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$ 320.16, found 320.20.

(*E*)-N-benzyl-3-(4-butylphenyl)-2-methyl-N-(propa-1,2-dien-1-yl)acrylamide. 11f was prepared following general procedure **GP-1b** from the corresponding enyne (232.0 mg, 0.7 mmol). Colourless oil (152.6 mg, 66% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.11 (m, 10H), 6.67 (s, 1H), 5.31 (d, J = 6.4 Hz, 2H), 4.83 (s, 2H), 2.68 – 2.58 (m, 2H), 2.16 (s, 3H), 1.67 – 1.55 (m, 2H), 1.39 (hex, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz,

3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.9 (Cq), 172.0 (Cq), 142.7 (Cq), 137.6 (Cq), 133.0 (CH), 132.1 (Cq), 131.1 (CH), 129.1 (2CH), 128.5 (4CH), 127.7 (2CH), 127.1 (2CH), 101.9 (CH), 87.3 (CH_2), 47.6 (CH_2), 35.4 (CH_2), 33.5 (CH_2), 22.4 (CH_2), 16.2 (CH_3), 14.0 (CH_3). **ESI-MS** calcd for $C_{24}H_{28}NO$ $[M+H]^+$ 346.22, found 346.25.

(*E*)-tert-butyl 3-(3-(benzyl(propa-1,2-dien-1-yl)amino)-2-methyl-3-oxoprop-1-en-1-yl)-2-methyl-1H-indole-1-carboxylate. 11g was prepared following general procedure **GP-1b** from the corresponding enyne (290.0 mg, 0.65 mmol). Red viscous oil (178.0 mg, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.3 Hz, 1H), 7.50 – 7.10 (m, 9H), 6.68 (brs, 1H), 5.37 – 5.30 (m, 2H), 4.90 (s, 2H), 2.51 (s, 3H), 1.95 (s, 3H), 1.72 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.2 (Cq), 171.3 (Cq), 150.6 (Cq), 137.5 (Cq), 135.7 (Cq), 135.3 (Cq), 134.7 (Cq), 128.8 (Cq), 128.5 (2CH), 127.7 (2CH), 127.2 (2CH), 123.8 (CH), 122.8 (CH), 118.8 (CH), 115.5 (CH), 114.8 (Cq), 102.0 (CH), 87.4 (CH_2), 84.1 (Cq), 47.4 (CH_2), 28.3 ($3CH_3$), 17.0 (CH_3), 15.6 (CH_3). **ESI-MS** calcd for $C_{28}H_{30}N_2NaO_3$ $[M+Na]^+$ 465.21, found 465.19.

(*E*)-N-(4-methoxybenzyl)-2-methyl-3-phenyl-N-(propa-1,2-dien-1-yl)acrylamide. 11h was prepared following general procedure **GP-1b** from the corresponding enyne (319.4 mg, 1.0 mmol). White solid (163.3 mg, 51% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.19 (m, 6H RotA, 6H RotB), 6.95 – 6.71 (m, 2H RotA, 2H RotB), 6.48 (q, *J* = 1.7 Hz, 1H RotB), 6.42 (q, *J* = 2.0 Hz, 1H RotA), 5.35 (d, *J* = 6.1 Hz, 2H RotA), 5.27 (d, *J* = 6.2 Hz, 2H RotB), 4.83 – 4.58 (m, 2H RotA, 2H RotB), 3.84 – 3.82 (m, 3H RotA, 3H RotB), 2.16 (br s, 3H RotA), 2.15 (br s, 3H RotB). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.0, 201.0, 171.0, 170.2, 158.8, 158.6, 135.7, 135.4, 132.2, 131.7, 130.0, 129.6, 129.1, 128.9, 128.7, 128.43, 128.38, 127.9, 127.8, 127.74, 127.68, 127.6, 113.8, 113.6, 100.5, 98.3, 87.3, 87.2, 55.33, 55.32, 49.3, 45.8, 22.2, 16.1. **ESI-MS** calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$ 320.16, found 320.09.

(*E*)-N-(4-fluorobenzyl)-2-methyl-3-phenyl-N-(propa-1,2-dien-1-yl)acrylamide. 11i was prepared following general procedure **GP-1b** from the corresponding enyne (245.9 mg, 0.8 mmol). White solid (192.0 mg, 49% yield). Two rotamers are observed due to the dynamic amide group. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.17 (m, 8H RotA, 8H RotB), 7.14 – 6.89 (m, 2H RotA, 3H RotB), 6.72 (br s, 1H RotA), 5.36 – 5.22 (m, 2H RotA, 2H RotB), 4.79 (s, 2H Rot A, 2H RotB), 2.16 (br s, 3H RotA, 3H RotB). **^{13}C NMR**

(101 MHz, $CDCl_3$) δ 200.8, 171.7, 170.2, 162.0 (d, *J* = 245.3 Hz), 135.5, 133.27 (d, *J* = 3.1 Hz), 131.9, 130.26 (d, *J* = 8.0 Hz), 129.3, 129.1, 128.4, 127.8, 127.7, 115.4, 115.2, 115.0, 101.8, 100.6, 87.5, 46.7, 22.1, 16.2. **^{19}F NMR (**565 MHz, $CDCl_3$) δ -115.31 (m). **ESI-MS** calcd for $C_{20}H_{19}FNO$ $[M+H]^+$ 308.14, found 308.24. (*Slow decomposition during the measurement of the NMR sample was observed*).

(*E*)-N-(cyanomethyl)-2-methyl-3-phenyl-N-(propa-1,2-dien-1-yl)acrylamide. 11j was prepared following general procedure **GP-1b** from the corresponding enyne (200.0 mg, 0.84 mmol). Pale yellow solid (68.6 mg, 34% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.28 (m, 5H), 7.12 (brs, 1H), 6.81 (brs, 1H), 5.63 (d, *J* = 6.3 Hz, 2H), 4.53 (s, 2H), 2.20 (d, *J* = 1.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.5, 171.1, 135.0, 134.3, 130.1, 129.3, 128.6, 128.3, 115.2, 100.7, 89.7, 32.3, 16.0. **ESI-MS** calcd for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.12, found 239.09.

(*E*)-N-cyclopropyl-2-methyl-3-phenyl-N-(propa-1,2-dien-1-yl)acrylamide. 11k was prepared following general procedure **GP-1b** from the corresponding enyne (239.2 mg, 1.0 mmol). Pale yellow liquid (123.4 mg, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.18 (m, 6H), 6.78 (s, 1H), 5.38 (d, *J* = 6.4 Hz, 2H), 2.71 (dt, *J* = 6.9, 3.0 Hz, 1H), 2.17 (d, *J* = 1.5 Hz, 3H), 0.95 – 0.88 (m, 2H), 0.77 (ddd, *J* = 3.9, 2.3, 1.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 202.8, 172.8, 136.0, 133.1, 132.3, 129.1, 128.4, 127.7, 100.6, 85.8, 29.6, 16.0, 9.8. **ESI-MS** calcd for $C_{16}H_{18}NO$ $[M+H]^+$ 240.14, found 240.19.

(R)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-6-phenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one. 10a was isolated following the **GP-2** using 7**a** as reagent (55.5 mg, 0.2 mmol). Yield **25%** (13.5 mg, 0.024 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.03 (m, 19H, Ar-H), 5.32 (d, *J* = 14.2 Hz, $H_{2'''}$), 4.83 (d, *J* = 15.1 Hz, $H_{3''}$), 4.47 (d, *J* = 15.0 Hz, $H_{3''}$), 4.28 – 4.21 (brs, $H_{9'}$), 4.03 – 3.72 (m, H_2, $H_{3'}$, $H_{3'}$, $H_{4'}$, $H_{2'''}$), 3.58 (dd, *J* = 22.1, 3.0 Hz, $H_{4'}$), 3.44 – 3.31 (m, H_6), 2.68 (q, *J* = 7.6 Hz, H_1), 2.09 – 1.87 (m, H_5, $2H_7$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (C_4), 170.1 ($C_{1'}$), 151.1 (Cq), 144.5 (Cq), 137.2 (Cq), 136.8 (Cq), 133.3 (Cq), 132.9 (Cq), 130.5 (Cq), 129.6 (CH), 129.0 (2CH), 128.9 (CH), 128.8 (4CH), 128.5 (2CH), 128.0 (2CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 127.1 (CH), 126.3 (2CH), 126.2 (CH), 66.2 (C_2), 52.2 ($C_{3'}$), 47.6 (C_5), 46.2 ($C_{3''}$), 45.0 ($C_{2'''}$), 42.8 (C_6), 38.5 ($C_{9'}$), 32.0 (C_7), 31.8 (C_1), 30.3

($C_{4'}$). **ESI-MS** calcd for $C_{38}H_{34}N_2NaO_2$ $[M+Na]^+$ 573.25, found 573.26. **ESI-HRMS** calcd for $C_{38}H_{34}N_2KO_2$ $[M+K]^+$ 589.2252, found 589.2260.

(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-6-phenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one. 10a' was isolated following the **GP-2** using **9a** as reagent (55.5 mg, 0.2 mmol). Yield **29%** (16.2 mg, 0.029 mmol).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.16 (m, 18H), 6.96 (d, *J* = 7.2 Hz, 1H), 5.52 (d, *J* = 15.1 Hz, 1H), 4.73 – 4.58 (m, 2H), 4.53 (d, *J* = 15.1 Hz, 1H), 4.35 (brs, 1H), 3.98 – 3.68 (m, 3H), 3.62 – 3.49 (m, 3H), 2.75 – 2.69 (m, 1H), 2.51 (q, *J* = 7.6 Hz, 1H), 2.11 – 1.96 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (Cq), 170.0 (Cq), 150.9 (Cq), 144.4 (Cq), 137.5 (Cq), 137.4 (Cq), 134.4 (Cq), 133.4 (Cq), 130.7 (Cq), 129.1 (CH), 129.0 (2CH), 128.9 (CH), 128.9 (2CH), 128.8 (CH), 128.7 (2CH), 128.5 (2CH), 128.2 (2CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 126.4 (CH), 126.2 (CH), 69.0 (CH), 52.0 (CH_2), 48.2 (CH), 46.2 (CH_2), 45.2 (CH_2), 42.9 (CH), 38.7 (CH), 31.8 (CH_2), 30.6 (CH), 30.5 (CH_2). **ESI-MS** calcd for $C_{38}H_{34}N_2NaO_2$ $[M+Na]^+$ 573.25, found 573.27. **ESI-HRMS** calcd for $C_{38}H_{35}N_2O_2$ $[M+H]^+$ 573.2693, found 573.2697.

(R)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-5-deutero-6-phenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one *d*$_1$-10a was isolated following the **GP-2** using ***d*$_1$-9a** as reagent (55.2 mg, 0.2 mmol). Yield **22**% (12.3 mg, 0.022 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 6.99 (m, 19H), 5.31 (d, *J* = 14.2 Hz, 1H), 4.82 (d, *J* = 15.0 Hz, 1H), 4.48 (d, *J* = 15.0 Hz, 1H), 4.25 (brs, 1H), 4.04 – 3.71 (m, 5H), 3.58 (dd, *J* = 22.1, 2.8 Hz, 1H), 3.37 (dd, *J* = 9.1, 3.8 Hz, 1H), 2.69 (t, *J* = 7.9 Hz, 1H), 2.10 – 2.02 (m, 1H), 1.99 – 1.89 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 177.2 (Cq), 170.1 (Cq), 151.1 (Cq), 144.5 (Cq), 137.2 (Cq), 136.8 (Cq), 133.3 (Cq), 133.0 (Cq), 130.5 (Cq), 129.6 (CH), 129.0 (2CH), 128.9 (CH), 128.83 (2CH), 128.82 (2CH), 128.5 (2CH), 128.0 (2CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 127.1 (CH), 126.3 (2CH), 126.1 (CH), 66.2 (CH), 52.2 (CH_2), 47.6 (CH, residual peak), 46.2 (CH_2), 45.0 (CH_2), 42.7 (CH), 38.5 (CH_2), 32.0 (CH_2), 31.7 (CH), 30.3 (CH_2). **ESI-HRMS** calcd for $C_{38}H_{34}DN_2O_2$ $[M+H]^+$ 552.2756, found 555.2748.

(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-5-deutero-6-phenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one *d*$_1$-10a' was isolated following the **GP-2** using ***d*$_1$-9a** as reagent (55.2 mg, 0.2 mmol). Yield **29**% (16.1 mg, 0.029 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.02 (m, 18H), 6.94 (d, *J* = 7.0 Hz, 1H), 5.50 (d, *J* = 15.1 Hz, 1H), 4.64 (q, *J* = 14.9 Hz, 2H), 4.50 (d, *J* = 15.1 Hz, 1H), 4.33 (brs, 1H), 3.90 (d, *J* = 19.1 Hz, 1H), 3.82 – 3.67 (m, 2H), 3.63 – 3.47 (m, 3H), 2.49 (t, *J* = 7.9 Hz, 1H), 2.10 – 1.95 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 175.7 (Cq), 170.0 (Cq), 150.9 (Cq), 144.4 (Cq), 137.5 (Cq), 137.4 (Cq), 134.5 (Cq), 133.4 (Cq), 130.7 (Cq), 129.1 (CH), 128.9 (2CH), 128.9 (CH), 128.8 (2CH), 128.7 (2CH), 128.5 (2CH), 128.2 (2CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 126.4 (2CH), 126.2 (CH), 69.0 (CH), 52.0 (CH_2), 48.3 (CH, residual peak), 46.2 (CH_2), 45.2 (CH_2), 42.8 (CH), 38.7 (CH), 31.8 (CH_2), 30.52 (CH), 30.5 (CH_2). **ESI-HRMS** calcd for $C_{38}H_{34}DN_2O_2$ $[M+H]^+$ 552.2756, found 555.2763.

(R)-2-benzyl-9-((1S,2S,5R,6S)-1-deutero-3-benzyl-4-oxo-6-pentadeuterophenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2,3,4,9-tetrahydro-5,6,7,8-tetradeutero-1H-benzo[f]isoindol-1-one *d*$_{10}$-10a was isolated following the **GP-2** using ***d*$_5$-9a** as reagent (56.0 mg, 0.2 mmol). Yield **26%** (14.8 mg, 0.026 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.15 (m, 10H), 5.31 (d, *J* = 14.2 Hz, 1H), 4.82 (d, *J* = 14.9 Hz, 1H), 4.48 (d, *J* = 15.0 Hz, 1H), 4.25 (s, 1H), 4.06 – 3.71 (m, 5H), 3.58 (dd, *J* = 22.1, 2.9 Hz, 1H), 3.44 – 3.33 (m, 1H), 2.17 – 1.86 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (Cq), 170.1 (Cq), 151.1 (Cq), 144.4 (Cq), 137.2 (Cq), 136.9 (Cq), 133.2 (Cq), 132.9 (Cq), 130.5 (Cq), 129.0 (2CH), 128.8 (2CH), 128.8 (2CH), 128.0 (2CH), 127.8 (CH), 127.7 (CH), 66.1 (CH), 52.2 (CH_2), 47.5 (CH), 46.2 (CH_2), 45.1 (CH_2), 42.8 (CH), 38.5 (CH), 31.9 (CH_2), 31.8 – 31.4 (m, CD), 30.2 (CH_2). **ESI-HRMS** calcd for $C_{38}H_{25}D_{10}N_2O_2$ $[M+H]^+$ 561.3321, found 561.3329.

(S)-2-benzyl-9-((1S,2S,5R,6S)-1-deutero-3-benzyl-4-oxo-6-pentadeuterophenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2,3,4,9-tetrahydro-5,6,7,8-tetradeutero-1H-benzo[f]isoindol-1-one *d*$_{10}$-10a' was isolated following the **GP-2** using ***d*$_5$-9a** as reagent (56.0 mg, 0.2 mmol). Yield **29%** (16.5 mg, 0.029 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.17 (m, 10H), 5.50 (d, *J* = 15.1 Hz, 1H), 4.64 (q, *J* = 14.9 Hz, 2H), 4.50 (d, *J* = 15.5 Hz, 1H), 4.33 (d, *J* = 3.9 Hz, 1H), 3.90 (d, *J* = 19.2 Hz, 1H), 3.80 – 3.67 (m, 2H),

3.62 – 3.46 (m, 3H), 2.71 (s, 1H), 2.08 – 1.93 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (Cq), 170.0 (Cq), 150.9 (Cq), 144.3 (Cq), 137.5 (Cq), 137.4 (Cq), 134.4 (Cq), 133.3 (Cq), 130.8 (Cq), 128.9 (2CH), 128.8 (2CH), 128.7 (2CH), 128.2 (2CH), 127.7 (CH), 127.6 (CH), 68.9 (CH), 52.0 (CH_2), 48.0 (CH), 46.2 (CH_2), 45.3 (CH_2), 42.8 (CH), 38.7 (CH), 31.7 (CH_2), 30.4 (CH_2). **ESI-HRMS** calcd for $C_{38}H_{25}D_{10}N_2O_2$ $[M+H]^+$ 561.3321, found 561.3331.

(R)-2-nonyl-9-((1S,2S,5R,6S)-3-nonyl-4-oxo-6-phenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10b was isolated following the **GP-2** using **9b** as reagent (62.3 mg, 0.2 mmol). Yield **15%** (9.3 mg, 0.015 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.12 (m, 6H), 7.11 (d, *J* = 7.3 Hz, 2H), 6.99 (d, *J* = 7.0 Hz, 1H), 4.20 – 4.03 (m, 3H), 4.02 – 3.91 (m, 1H), 3.89 (dd, *J* = 22.1, 3.9 Hz, 1H), 3.68 (dd, *J* = 22.2, 3.2 Hz, 1H), 3.59 (dd, *J* = 14.4, 7.0 Hz, 1H), 3.42 (dt, *J* = 13.9, 7.0 Hz, 2H), 3.19 (ddd, *J* = 13.5, 8.7, 5.2 Hz, 1H), 2.45 (q, *J* = 7.2 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.21 (dtd, *J* = 12.5, 6.9, 3.5 Hz, 1H), 1.93 (d, *J* = 6.7 Hz, 1H), 1.91 – 1.71 (m, 3H), 1.66 – 1.58 (m, 2H), 1.40 – 1.23 (m, 24H), 0.94 – 0.85 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.1 (Cq), 170.1 (Cq), 149.8 (Cq), 144.5 (Cq), 133.0 (Cq), 132.1 (Cq), 130.8 (Cq), 129.5 (CH), 128.9 (CH), 128.4 (2CH), 127.3 (CH), 127.0 (CH), 126.3 (2CH), 126.1 (CH), 66.2 (CH), 52.7 (CH_2), 47.8 (CH), 42.6 (CH), 42.2 (CH_2), 40.7 (CH_2), 37.2 (CH), 32.6 (CH_2), 31.89 (CH_2), 31.85 (CH_2), 31.0 (CH), 30.1 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.34 (CH_2), 29.29 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 27.3 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 22.71 (CH_2), 22.67 (CH_2), 14.14 (CH_3), 14.12 (CH_3). **ESI-HRMS** calcd for $C_{42}H_{59}N_2O_2$ $[M+H]^+$ 623.4571, found 623.4564.

(S)-2-nonyl-9-((1S,2S,5R,6S)-3-nonyl-4-oxo-6-phenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10b' was isolated following the **GP-2** using **9b** as reagent (62.3 mg, 0.2 mmol). Yield **21%** (13.1 mg, 0.021 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.13 (m, 9H), 4.22 (s, 1H), 4.13 – 3.96 (m, 2H), 3.90 – 3.81 (m, 2H), 3.64 (dd, *J* = 21.9, 2.5 Hz, 1H), 3.48 (quint, *J* = 7.4 Hz, 2H), 3.43 – 3.33 (m, 1H), 3.31 – 3.17 (m, 1H), 2.72 (q, *J* = 7.6 Hz, 1H), 2.64 (d, *J* = 6.8 Hz, 1H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.80 – 1.60 (m, 2H), 1.58 – 1.49 (m, 2H), 1.37 – 1.17 (m, 24H), 0.96 – 0.82 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.9 (Cq), 169.8 (Cq), 149.9 (Cq), 144.6 (Cq), 134.5 (Cq), 133.7 (Cq), 131.4 (Cq), 129.1 (CH), 129.0 (CH), 128.5 (2CH), 127.2 (CH),

127.1 (CH), 126.4 (CH), 126.2 (2CH), 69.4 (CH), 52.6 (CH_2), 48.2 (CH), 42.9 (CH), 42.3 (CH_2), 41.2 (CH_2), 39.6 (CH), 32.4 (CH_2), 31.9 (CH), 31.8 (CH_2), 31.6 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 22.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 14.1 (CH_3). **ESI-HRMS** calcd for $C_{42}H_{59}N_2O_2$ $[M+H]^+$ 623.4571, found 623.4580.

(R)-9-((1S,2S,5R,6S)-4-oxo-3-phenethyl-6-phenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2-phenethyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10c was isolated following the **GP-2** using **9c** as reagent (57.9 mg, 0.2 mmol). Yield **26%** (14.9 mg, 0.026 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 2H), 7.37 – 7.10 (m, 15H), 7.03 (d, *J* = 7.4 Hz, 2H), 4.47 (dt, *J* = 13.8, 8.3 Hz, 1H), 4.14 (s, 1H), 3.99 (s, 1H), 3.89 – 3.67 (m, 5H), 3.55 (dd, *J* = 22.2, 3.3 Hz, 1H), 3.44 (dt, *J* = 12.2, 5.6 Hz, 1H), 3.28 – 3.21 (m, 2H), 3.16 – 3.07 (m, 1H), 2.99 – 2.91 (m, 2H), 2.28 (q, *J* = 7.2 Hz, 1H), 1.99 (ddt, *J* = 13.0, 7.0, 2.8 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.74 – 1.66 (m, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (Cq), 170.0 (Cq), 149.9 (Cq), 144.5 (Cq), 138.8 (Cq), 138.3 (Cq), 133.0 (Cq), 132.1 (Cq), 130.6 (Cq), 129.4 (CH), 129.1 (2CH), 128.9 (CH), 128.7 (2CH), 128.6 (2CH), 128.5 (2CH), 128.4 (2CH), 127.3 (CH), 127.0 (CH), 126.6 (CH), 126.5 (CH), 126.3 (2CH), 126.1 (CH), 66.3 (CH), 53.4 (CH_2), 47.7 (CH), 43.9 (CH_2), 42.4 (CH), 40.8 (CH_2), 37.2 (CH), 35.1 (CH_2), 32.9 (CH_2), 32.1 (CH_2), 30.6 (CH), 30.0 (CH_2). **ESI-HRMS** calcd for $C_{40}H_{38}N_2NaO_2$ $[M+Na]^+$ 601.2855, found 601.2862.

(S)-9-((1S,2S,5R,6S)-4-oxo-3-phenethyl-6-phenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2-phenethyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10c' was isolated following the **GP-2** using **9c** as reagent (57.9 mg, 0.2 mmol). Yield **22%** (12.8 mg, 0.022 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.14 (m, 18H), 7.06 – 7.01 (m, 1H), 4.50 (dt, *J* = 14.1, 6.9 Hz, 1H), 4.16 (brs, 1H), 3.81 – 3.43 (m, 7H), 3.31 (d, *J* = 8.9 Hz, 1H), 3.08 (q, *J* = 7.1 Hz, 2H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.50 (d, *J* = 6.6 Hz, 1H), 2.41 (q, *J* = 7.1 Hz, 1H), 1.95 (tq, *J* = 8.9, 3.2 Hz, 1H), 1.74 (ddd, *J* = 12.8, 9.1, 7.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.9 (Cq), 169.8 (Cq), 150.3 (Cq), 144.7 (Cq), 139.3 (Cq), 139.0 (Cq), 134.4 (Cq), 133.5 (Cq), 130.9 (Cq), 129.0 (CH), 128.93 (2CH), 128.92 (CH), 128.8 (2CH), 128.6 (4CH), 128.5 (2CH), 127.2 (CH), 127.0 (CH), 126.5 (CH), 126.40 (CH), 126.38 (2CH), 126.2 (CH), 70.2 (CH), 53.5 (CH_2), 47.8 (CH), 43.8, 42.7 (CH), 41.9

(CH_2), 39.1 (CH), 35.1 (CH_2), 33.9 (CH_2), 31.9 (CH_2), 30.9 (CH), 30.4 (CH_2). **ESI-HRMS** calcd for $C_{40}H_{38}N_2NaO_2$ $[M+Na]^+$ 601.2855, found 601.2861.

(S)-9-((1S,2S,5R,6S)-4-oxo-3,6-diphenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2-phenyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10d' was isolated following the **GP-2** using **9d** as reagent (57.5 mg, 0.22 mmol). Yield **17%** (9.7 mg, 0.022 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.9 Hz, 2H), 7.80 (dd, *J* = 8.7, 1.0 Hz, 2H), 7.66 – 6.95 (m, 15H), 5.01 (d, *J* = 2.0 Hz, 1H), 4.64 (d, *J* = 18.2 Hz, 1H), 4.42 (dd, *J* = 18.3, 2.0 Hz, 1H), 4.34 (brs, 1H), 3.99 (dd, *J* = 22.4, 4.1 Hz, 1H), 3.77 (dd, *J* = 22.5, 3.5 Hz, 1H), 3.52 (dt, *J* = 8.5, 4.0 Hz, 1H), 2.54 – 2.44 (m, 2H), 2.42 – 2.32 (m, 1H), 2.17 – 2.14 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (Cq), 169.1 (Cq), 150.0 (Cq), 144.1 (Cq), 139.1 (Cq), 138.2 (Cq), 132.4 (Cq), 131.8 (Cq), 131.7 (Cq), 129.6 (CH), 129.5 (2CH), 129.3 (2CH), 129.0 (CH), 128.5 (2CH), 127.6 (CH), 127.2 (CH), 126.3 (2CH), 125.0 (CH), 124.3 (CH), 122.6 (CH), 121.5 (2CH), 118.8 (2CH), 67.0 (CH), 53.3 (CH_2), 49.1 (CH), 42.6 (CH), 37.0 (CH), 32.8 (CH_2), 30.0 (CH_2), 29.7 (CH). **ESI-HRMS** calcd for $C_{40}H_{38}N_2NaO_2$ $[M+Na]^+$ 545.2199, found 545.2206.

(R)-2-cyclopropyl-9-((1S,2S,5R,6S)-3-cyclopropyl-4-oxo-6-phenyl-3-azabicyclo[3.2.0]heptan-2-yl)-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10e was isolated following the **GP-2** using **9e** as reagent (45.1 mg, 0.2 mmol). Yield **24%** (10.8 mg, 0.024 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 6.99 (m, 9H), 4.25 (brs, 1H), 4.07 (d, *J* = 19.1 Hz, 1H), 3.97 – 3.82 (m, 3H), 3.65 (dd, *J* = 22.2, 3.3 Hz, 1H), 3.38 – 3.27 (m, 1H), 2.93 – 2.85 (m, 1H), 2.83 – 2.73 (m, 1H), 2.42 (q, *J* = 8.0 Hz, 1H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.92 (d, *J* = 8.4 Hz, 1H), 1.21 – 1.12 (m, 2H), 1.03 – 0.70 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.5 (Cq), 171.5 (Cq), 150.2 (Cq), 144.4 (Cq), 132.9 (Cq), 132.0 (Cq), 131.1 (Cq), 129.6 (CH), 129.0 (CH), 128.4 (2CH), 127.3 (CH), 127.1 (CH), 126.3 (2CH), 126.1 (CH), 67.9 (CH), 53.4 (CH_2), 48.4 (CH), 42.3 (CH), 38.4 (CH), 32.6 (CH_2), 30.9 (CH), 30.1 (CH_2), 24.7 (CH), 24.6 (CH_2), 7.8 (CH_2), 5.6 (CH_2), 5.4 (CH_2), 5.2 (CH_2). **ESI-HRMS** calcd for $C_{30}H_{30}N_2NaO_2$ $[M+Na]^+$ 473.2199, found 473.2191.

(S)-6-chloro-9-((1S,2S,5R,6S)-6-(4-chlorophenyl)-3-cyclopropyl-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-2-cyclopropyl-2,3,4,9-tetrahydro-1H-

benzo[f]isoindol-1-one 10e' was isolated following the **GP-2** using **9e** as reagent (45.1 mg, 0.2 mmol). Yield **30%** (13.5 mg, 0.030 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (m, 9H), 4.28 (brs, 1H), 3.97 (d, *J* = 19.0 Hz, 1H), 3.83 (d, *J* = 20.4 Hz, 2H), 3.74 (d, *J* = 3.0 Hz, 1H), 3.62 (dd, *J* = 21.9, 2.6 Hz, 1H), 3.41 – 3.31 (m, 1H), 3.12 (tt, *J* = 7.5, 4.1 Hz, 1H), 2.81 – 2.70 (m, 2H), 2.60 (d, *J* = 6.7 Hz, 1H), 2.28 – 2.15 (m, 1H), 2.13 – 2.02 (m, 1H), 1.14 (ddd, *J* = 12.3, 9.6, 6.8 Hz, 2H), 0.97 – 0.64 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.3 (Cq), 171.2 (Cq), 150.1 (Cq), 144.4 (Cq), 134.3 (Cq), 133.6 (Cq), 131.6 (Cq), 129.2 (CH), 129.0 (CH), 128.5 (2CH), 127.2 (CH), 127.2 (CH), 126.4 (CH), 126.3 (2CH), 71.5 (CH), 53.2 (CH_2), 48.8 (CH), 42.6 (CH), 40.5 (CH), 32.4 (CH_2), 31.8 (CH), 30.5 (CH_2), 24.8 (CH), 24.6 (CH), 8.7 (CH_2), 5.8 (CH_2), 5.6 (CH_2), 4.9 (CH_2). **ESI-HRMS** calcd for $C_{30}H_{30}N_2NaO_2$ $[M+Na]^+$ 473.2199, found 473.2208.

(R)-6-chloro-9-((1S,2S,5R,6S)-6-(4-chlorophenyl)-4-oxo-3-phenethyl-3-azabicyclo[3.2.0]heptan-2-yl)-2-phenethyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10f was isolated following the **GP-2** using **9f** as reagent (65.0 mg, 0.2 mmol). Yield **15%** (9.7 mg, 0.015 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.35 – 7.13 (m, 13H), 6.96 (d, *J* = 8.4 Hz, 2H), 4.47 (dt, *J* = 13.8, 8.3 Hz, 1H), 4.09 (brs, 1H), 3.99 (s, 1H), 3.84 – 3.67 (m, 5H), 3.61 – 3.54 (m, 1H), 3.41 (dt, *J* = 13.1, 6.2 Hz, 1H), 3.23 (t, *J* = 7.6 Hz, 2H), 3.09 – 3.00 (m, 1H), 2.99 – 2.90 (m, 2H), 2.20 (dt, *J* = 13.0, 6.3 Hz, 1H), 2.10 – 1.89 (m, 2H), 1.71 – 1.57 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8 (Cq), 169.7 (Cq), 149.2 (Cq), 142.7 (Cq), 138.7 (Cq), 138.0 (Cq), 135.0 (Cq), 133.2 (Cq), 131.9 (Cq), 130.7 (Cq), 130.53 (CH), 130.50 (Cq), 129.1 (2CH), 128.9 (CH), 128.67 (2CH), 128.66 (2CH), 128.53 (2CH), 128.50 (2CH), 127.7 (2CH), 127.3 (CH), 126.63 (CH), 126.59 (CH), 66.1 (CH), 53.3 (CH_2), 47.8 (CH), 43.9 (CH_2), 41.9 (CH), 40.7 (CH_2), 36.8 (CH), 35.0 (CH_2), 32.8 (CH_2), 31.9 (CH_2), 30.3 (CH), 29.4 (CH_2). **ESI-HRMS** calcd for $C_{40}H_{37}Cl_2N_2O_2$ $[M+H]^+$ 647.2267, found 647.2274.

(S)-6-chloro-9-((1S,2S,5R,6S)-6-(4-chlorophenyl)-4-oxo-3-phenethyl-3-azabicyclo[3.2.0]heptan-2-yl)-2-phenethyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10f' was isolated following the **GP-2** using **9f** as reagent (65.0 mg, 0.2 mmol). Yield **17%** (10.9 mg, 0.017 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.06 (m, 16H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.51 (dt, *J* = 13.8, 6.6 Hz, 1H), 4.13 (s, 1H), 3.84 – 3.73 (m, 1H), 3.72 – 3.53 (m, 5H), 3.53 – 3.42 (m, 2H), 3.30 (d, *J* = 7.9 Hz, 1H), 3.16 – 2.98 (m, *J* =

6.6 Hz, 2H), 2.88 (t, *J* = 6.6 Hz, 2H), 2.47 (d, *J* = 7.1 Hz, 1H), 2.34 (q, *J* = 7.2 Hz, 1H), 1.95 (t, *J* = 10.6 Hz, 1H), 1.83 – 1.68 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.7 (Cq), 169.4 (Cq), 149.6 (Cq), 142.8 (Cq), 139.3 (Cq), 138.8 (Cq), 135.3 (Cq), 132.9 (Cq), 132.8 (Cq), 132.0 (Cq), 130.7 (Cq), 130.2 (CH), 128.9 (2CH), 128.8 (CH), 128.7 (2CH), 128.7 (2CH), 128.63 (2CH), 128.62 (2CH), 127.8 (2CH), 127.5 (CH), 126.6 (CH), 126.5 (CH), 70.2 (CH), 53.4 (CH_2), 47.8 (CH), 43.8 (CH_2), 42.2 (CH), 42.0 (CH_2), 38.5 (CH), 35.0 (CH_2), 33.9 (CH_2), 31.7 (CH_2), 30.7 (CH), 30.2 (CH_2). **ESI-HRMS** calcd for $C_{40}H_{37}Cl_2N_2O_2$ $[M+H]^+$ 647.2267, found 647.2259.

(*R*)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-6-(4-bromophenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-6-bromo-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 8g was isolated with traces of **10g'** following the **GP-2** using **9g** as reagent (59.2 mg, 0.167 mmol). Yield **17%** (10.9 mg, 0.014 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.29 (m, 12H), 7.24 (dd, *J* = 7.5, 1.8 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, $H_{8'}$), 5.31 (d, *J* = 14.2 Hz, $H_{3''}$), 4.83 (d, *J* = 14.9 Hz, $H_{2'''}$), 4.50 (d, *J* = 14.9 Hz, $H_{2'''}$), 4.21 (brs, $H_{9'}$), 4.05 – 3.74 (m, H_2, $H_{3'''}$, $H_{3'}$, $H_{3'}$, $H_{4'}$), 3.57 (dd, *J* = 22.2, 2.8 Hz, $H_{4'}$), 3.36 (dt, *J* = 6.5, 3.1 Hz, H_6), 2.62 (q, *J* = 7.5 Hz, H_1), 2.13 – 2.01 (m, H_5, H_7), 2.02 – 1.90 (m, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8 (C_4), 169.7 ($C_{1'}$), 150.3 (Cq), 143.2 (Cq), 137.0 (Cq), 136.5 (Cq), 135.6 (Cq), 131.9 (Cq), 131.8 (CH), 131.6 (2CH), 131.0 ($C_{8'}$), 130.3 (Cq), 130.2 (CH), 129.0 (2CH), 128.9 (2CH), 128.9 (2CH), 128.1 (2CH), 128.0 (2CH), 128.0 (CH), 127.8 (CH), 121.4 (Cq), 120.0 (Cq), 66.0 (C_2), 52.1 ($C_{3'}$), 47.6 (C_5), 46.2 ($C_{2'''}$), 45.2 ($C_{3''}$), 42.3 (C_6), 38.1 ($C_{9'}$), 31.8 (C_7), 31.5 (C_1), 30.0 ($C_{4'}$). **ESI-MS** calcd for $C_{38}H_{32}Br_2N_2NaO_2$ $[M+Na]^+$ 731.07, found 731.14. **ESI-HRMS** calcd for $C_{38}H_{32}{}^{79}Br_2N_2KO_2$ $[M+K]^+$ 745.0462, found 745.0455.

(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-6-(4-bromophenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-6-bromo-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one. 10g' was isolated following the **GP-2** using **9g** as reagent (59.2 mg, 0.167 mmol). Yield **27%** (16.0 mg, 0.022 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.21 (m, 14H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, H_8), 5.50 (d, *J* = 15.1 Hz, $H_{3''}$), 4.71 – 4.58 (m, $2H_{2'''}$), 4.51 (d, *J* = 15.2 Hz, $H_{3''}$), 4.32 – 4.25 (m, $H_{9'}$), 3.91 (d, *J* = 19.2 Hz, H_3), 3.80 – 3.68 (m, H_4, H_3), 3.58 – 3.47 (m, H_6, H_4, H_2), 2.63 (d, *J* = 6.6 Hz, H_5), 2.42 (q, *J* = 7.3 Hz, H_1), 2.11 – 1.96 (m, $2H_7$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4 (C_4), 169.6 ($C_{1'}$),

150.1 (Cq), 143.1 (Cq), 137.3 (Cq), 137.1 (Cq), 136.4 (Cq), 135.6 (Cq), 133.4 (Cq), 131.7 (CH), 131.6 (2CH), 130.5 (CH), 130.5 (CH), 129.0 (2CH), 128.9 (2CH), 128.7 (2CH), 128.2 (2CH), 128.2 (2CH), 127.8 (CH), 127.7 (CH), 120.9 (Cq), 120.0 (Cq), 68.8 (C_2), 51.9 ($CH_{3'}$), 48.2 (C_5), 46.2 ($C_{2''}$), 45.3 ($C_{3''}$), 42.4 (C_6), 38.3 ($C_{9'}$), 31.5 (C_7), 30.5 (C_1), 30.2 ($C_{4'}$). **ESI-HRMS** calcd for $C_{38}H_{32}{}^{79}Br_2N_2NaO_2$ $[M+Na]^+$ 729.0723, found 745.0717.

(R)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-6-(4-methoxyphenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-6-methoxy-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10h was isolated following the **GP-2** using **9h** as reagent (61.1 mg, 0.2 mmol). Yield **18%** (11.0 mg, 0.018 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.37 – 7.21 (m, 6H), 7.07 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.86 – 6.78 (m, 3H), 6.76 (d, *J* = 2.6 Hz, 1H), 5.34 (d, *J* = 13.6 Hz, 1H), 4.85 (d, *J* = 15.0 Hz, 1H), 4.49 (d, *J* = 15.0 Hz, 1H), 4.22 (brs, 1H), 4.04 (d, *J* = 14.2 Hz, 1H), 3.95 (d, *J* = 19.1 Hz, 1H), 3.88 (d, *J* = 2.2 Hz, 1H), 3.85 – 3.75 (m, 8H), 3.55 (dd, *J* = 22.1, 2.8 Hz, 1H), 3.35 (dt, *J* = 6.4, 3.1 Hz, 1H), 2.60 (q, *J* = 7.5 Hz, 1H), 2.16 – 1.91 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (Cq), 170.1 (Cq), 158.7 (Cq), 157.9 (Cq), 150.7 (Cq), 137.2 (Cq), 136.9 (Cq), 136.7 (Cq), 134.6 (Cq), 130.9 (Cq), 130.5 (CH), 129.0 (2CH), 128.8 (4CH), 128.0 (2CH), 127.8 (CH), 127.7 (CH), 127.3 (2CH), 124.8 (Cq), 114.4 (CH), 113.8 (2CH), 112.3 (CH), 66.2 (CH), 55.3 ($2CH_3$), 52.2 (CH_2), 48.0 (CH), 46.2 (CH_2), 45.0 (CH_2), 42.2 (CH), 37.5 (CH), 32.2 (CH_2), 31.5 (CH), 30.5 (CH_2). **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_4$ $[M+H]^+$ 611.2904, found 611.2897.

(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-6-(4-methoxyphenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-6-methoxy-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10h' was isolated with traces of **10h** following the **GP-2** using **9h** as reagent (61.1 mg, 0.2 mmol). Yield **29%** (17.6 mg, 0.029 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.27 (m, 9H), 7.25 – 7.20 (m, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.88 – 6.80 (m, 2H), 6.75 – 6.70 (m, 2H), 5.50 (d, *J* = 15.1 Hz, 1H), 4.75 – 4.55 (m, 2H), 4.50 (d, *J* = 15.2 Hz, 1H), 4.28 (brs, 1H), 3.88 (d, *J* = 18.9 Hz, 1H), 3.81 – 3.68 (m, 8H), 3.60 – 3.46 (m, 3H), 2.67 (d, *J* = 6.8 Hz, 1H), 2.51 (q, *J* = 7.4 Hz, 1H), 2.12 – 1.91 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.9 (Cq), 170.0 (Cq), 158.4 (Cq), 158.0 (Cq), 150.6 (Cq), 137.5 (Cq), 137.4 (Cq), 136.6 (Cq), 134.6 (Cq), 131.1 (Cq), 129.9 (CH), 128.9 (2CH), 128.8 (2CH), 128.7

(2CH), 128.2 (2CH), 127.7 (CH), 127.6 (CH), 127.4 (2CH), 126.5 (Cq), 113.9 (CH), 113.7 (2CH), 113.2 (CH), 68.9 (CH), 55.3 (CH_3), 55.3 (CH_3), 52.0 (CH_2), 48.5 (CH), 46.2 (CH_2), 45.3 (CH_2), 42.3 (CH), 38.0 (CH), 32.0 (CH_2), 30.7 (CH), 30.7(CH_2). **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_4$ $[M+H]^+$ 611.2904, found 611.2910.

(R)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-6-(o-tolyl)-3-azabicyclo[3.2.0]heptan-2-yl)-8-methyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10i was isolated with traces of an additional isomer following the **GP-2** using **9i** as reagent (59.7 mg, 0.206 mmol). Yield **25%** (14.9 mg, 0.025 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.07 (m, 15H), 6.87 – 6.82 (m, 2H), 5.00 (d, *J* = 14.1 Hz, 1H), 4.74 (d, *J* = 14.8 Hz, 1H), 4.49 (d, *J* = 14.9 Hz, 1H), 4.29 (s, 1H), 3.98 (d, *J* = 19.2 Hz, 1H), 3.79 – 3.63 (m, 3H), 3.61 – 3.45 (m, 3H), 2.66 – 2.52 (m, 2H), 2.37 (s, 3H), 2.24 (s, 3H), 2.13 – 2.06 (m, 1H), 1.83 – 1.73 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.1 (Cq), 170.5 (Cq), 153.6 (Cq), 142.0 (Cq), 137.4 (Cq), 136.6 (Cq), 136.6 (Cq), 135.8 (Cq), 135.5 (Cq), 134.7 (Cq), 131.0 (Cq), 130.2 (CH), 129.5 (CH), 128.82 (2CH), 128.79 (2CH), 128.5 (2CH), 128.0 (2CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 126.9 (CH), 126.4 (CH), 126.2 (CH), 124.3 (CH), 64.2 (CH), 52.1 (CH_2), 47.2 (CH), 46.3 (CH_2), 46.1 (CH_2), 40.1 (CH), 40.0 (CH), 33.5 (CH), 31.3 (CH_2), 29.9 (CH_2), 19.7 (CH_3), 19.6 (CH_3). **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_2$ $[M+H]^+$ 579.3006, found 579.3011.

(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-6-(o-tolyl)-3-azabicyclo[3.2.0]heptan-2-yl)-8-methyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10i' was isolated following the **GP-2** using **9i** as reagent (59.7 mg, 0.206 mmol). Yield **36%** (21.6 mg, 0.037 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.03 (m, 17H), 5.60 (d, *J* = 15.5 Hz, 1H), 4.75 – 4.58 (m, 3H), 4.56 (brs, 1H), 3.92 (d, *J* = 19.1 Hz, 1H), 3.84 – 3.66 (m, 3H), 3.61 – 3.45 (m, 2H), 2.67 (d, *J* = 6.6 Hz, 1H), 2.52 (dt, *J* = 16.3, 8.1 Hz, 1H), 2.32 (s, 3H), 2.16 (s, 3H), 2.13 – 2.01 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.0 (Cq), 170.1 (Cq), 151.1 (Cq), 141.5 (Cq), 137.6 (Cq), 137.5 (Cq), 136.8 (Cq), 136.3 (Cq), 134.1 (Cq), 133.2 (Cq), 131.8 (Cq), 130.6 (CH), 129.5 (CH), 128.8 (2CH), 128.8 (2CH), 128.6 (2CH), 128.0 (2CH), 127.6 (2CH), 127.04 (CH), 126.95 (CH), 126.3 (CH), 125.8 (CH), 123.4 (CH), 66.4 (CH), 51.9 (CH_2), 47.0 (CH), 46.2 (CH_2), 45.0 (CH_2), 40.2 (CH), 35.5 (CH), 31.6 (CH_2), 30.6 (CH), 30.2 (CH_2), 19.6 (CH_3), 19.5 (CH_3). **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_2$ $[M+H]^+$ 579.3006, found 579.3013.

(R)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-6-(m-tolyl)-3-azabicyclo[3.2.0]heptan-2-yl)-5-methyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one (A) compound with **(R)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-6-(m-tolyl)-3-azabicyclo[3.2.0]heptan-2-yl)-7-methyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one (B) 10j$_A$/10j$_B$** mixture was isolated following the **GP-2** using **9j** as reagent (58.1 mg, 0.20 mmol). Yield **25%** (14.5 mg, 0.025 mmol, ^{1}H NMR ratio: 1:0.65). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 6.84 (m, 17H$_A$, 17H$_B$), 5.35 – 5.22 (m, 1H$_A$, 1H$_B$), 4.86 (d, *J* = 15.0 Hz, 1H$_B$), 4.82 (d, *J* = 15.0 Hz, 1H$_A$), 4.57 – 4.45 (m, 1H$_A$, 1H$_B$), 4.28 (brs, 1H$_B$), 4.20 (brs, 1H$_A$), 4.05 – 3.72 (m, 5H$_A$, 4H$_B$), 3.65 – 3.46 (m, 1H$_A$, 2H$_B$), 3.41 – 3.32 (m, 1H$_A$, 1H$_B$), 2.80 (q, *J* = 7.7 Hz, 1H$_A$), 2.70 (q, *J* = 7.5 Hz, 1H$_B$), 2.41 – 2.26 (m, 6H$_A$, 6H$_B$), 2.25 – 1.84 (m, 3H$_A$, 3H$_B$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.33 (Cq), 177.32 (Cq), 170.23 (Cq), 170.18 (Cq), 151.5 (Cq), 150.7 (Cq), 144.6 (Cq), 144.5 (Cq), 138.03 (Cq), 138.00 (Cq), 137.3 (Cq), 137.2 (Cq), 137.0 (Cq), 136.9 (Cq), 136.7 (Cq), 136.2 (Cq), 133.1 (Cq), 132.8 (Cq), 131.9 (Cq), 130.5 (Cq), 130.4 (Cq), 130.3 (CH), 130.2 (Cq), 129.04 (CH), 128.99 (CH), 128.82 (CH), 128.78 (CH), 128.7 (CH), 128.6 (CH), 128.40 (CH), 128.37 (CH), 128.1 (CH), 128.0 (CH), 127.77 (CH), 127.75 (CH), 127.65 (CH), 127.64 (CH), 127.4 (CH), 127.3 (CH), 126.9 (CH), 126.86 (CH), 126.84 (CH), 123.2 (CH), 123.1 (CH), 66.4 (CH), 66.3 (CH), 52.3 (CH_2), 52.2 (CH_2), 47.6 (CH), 47.5 (CH), 46.19 (CH_2), 46.18 (CH_2), 45.2 (CH_2), 45.0 (CH_2), 42.9 (CH), 42.7 (CH), 38.9 (CH_2), 38.7 (CH_2), 32.01 (CH), 31.96 (CH_2), 31.93 (CH_2), 31.89 (CH), 29.9 (CH_2), 28.2 (CH_2), 21.47 (CH_3), 21.46 (CH_3), 21.1 (CH_3), 19.9 (CH_3). **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_2$ $[M+H]^+$ 579.3006, found 579.3012.

(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-6-(m-tolyl)-3-azabicyclo[3.2.0]heptan-2-yl)-5-methyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one compound with **(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-4-oxo-6-(m-tolyl)-3-azabicyclo[3.2.0]heptan-2-yl)-7-methyl-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10j'$_A$/10j'$_B$** mixture was isolated following the **GP-2** using **9j** as reagent (58.1 mg, 0.20 mmol). Yield **29%** (16.7 mg, 0.029 mmol, ^{1}H NMR ratio: 0.91:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 6.90 (m, 16H$_A$, 16H$_B$), 6.78 (dd, *J* = 6.8, 1.9 Hz, 1H$_B$), 6.71 (s, 1H$_A$), 5.51 (d, *J* = 15.1 Hz, 1H$_A$, 1H$_B$), 4.71 – 4.57 (m, 2H$_A$, 2H$_B$), 4.59 – 4.46 (m, 1H$_A$, 1H$_B$), 4.34 (brs, 1H$_B$), 4.27 (s, 1H$_A$), 3.96 – 3.81 (m, 1H$_A$, 1H$_B$), 3.77 – 3.62 (m, 2H$_A$, 1H$_B$), 3.58 – 3.43 (m, 3H$_A$, 4H$_B$), 2.74 – 2.63 (m, 1H$_A$, 1H$_B$), 2.52 – 2.37 (m, 1H$_A$, 1H$_B$), 2.34 – 1.91 (m, 8H$_A$, 8H$_B$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.84 (Cq), 175.82 (Cq),

170.1 (Cq), 170.0 (Cq), 151.1 (Cq), 150.5 (Cq), 144.33 (Cq), 144.28 (Cq), 138.07 (Cq), 138.05 (Cq), 137.6 (2Cq), 137.5 (Cq), 137.4 (Cq), 136.8 (Cq), 136.2 (Cq), 134.4 (Cq), 134.3 (Cq), 131.9 (Cq), 130.7 (Cq), 130.4 (Cq), 130.3 (Cq), 129.6 (CH), 128.91 (CH), 128.88 (CH), 128.83 (CH), 128.82 (CH), 128.78 (CH), 128.75 (CH), 128.69 (CH), 128.6 (CH), 128.40 (CH), 128.37 (CH), 128.19 (CH), 128.16 (CH), 127.9 (CH), 127.64 (CH), 127.62 (CH), 127.58 (CH), 127.56 (CH), 127.49 (CH), 127.47 (CH), 127.0 (CH), 126.91 (CH), 126.89 (CH), 126.87 (CH), 123.1 (CH), 69.4 (CH), 69.1 (CH), 52.1 (CH_2), 52.0 (CH_2), 48.2 (CH), 48.1 (CH), 46.2 (CH_2), 45.3 (CH_2), 45.2 (CH_2), 42.8 (CH), 42.7 (CH), 38.7 (CH), 38.6 (CH), 31.7 (CH_2), 31.6 (CH_2), 30.6 (CH), 30.4 (CH), 30.1 (CH_2), 28.3 (CH_2), 21.5 ($2CH_3$), 21.0 (CH_3), 19.9 (CH_3). **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_2$ $[M+H]^+$ 579.3006, found 579.3000.

(R)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-6-(3-methoxyphenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-5-methoxy-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one compound with **(R)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-6-(3-methoxyphenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-7-methoxy-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one $10k_A/10k_B$** mixture was isolated following the **GP-2** using **9k** as reagent (61.1 mg, 0.20 mmol). Yield **28%** (17.0 mg, 0.028 mmol, ^{1}H NMR ratio: 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, $2H_A$, $2H_B$), 7.39 (t, J = 7.6 Hz, $2H_A$, $2H_B$), 7.35 – 7.08 (m, $8H_A$, $8H_B$), 6.84 – 6.76 (m, $1H_A$, $1H_B$), 6.75 – 6.63 (m, $4H_A$, $3H_B$), 6.57 (d, J = 2.6 Hz, H_B), 5.30 (d, J = 14.2 Hz, H_A), 5.26 (d, J = 14.1 Hz, H_B), 4.84 (d, J = 7.6 Hz, H_A), 4.80 (d, J = 7.6 Hz, H_B), 4.49 (d, J = 8.0 Hz, H_B), 4.45 (d, J = 8.1 Hz, H_A), 4.25 (s, H_A), 4.18 (s, H_B), 4.11 – 3.40 (m, $12H_A$, $12H_B$), 3.35 (t, J = 7.8 Hz, H_A, H_B), 2.76 – 2.59 (m, H_A, H_B), 2.13 – 1.86 (m, $3H_A$, $3H_B$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.24 (Cq), 177.21 (Cq), 170.3 (Cq), 170.2 (Cq), 159.69 (Cq), 159.68 (Cq), 158.2 (Cq), 156.9 (Cq), 151.6 (Cq), 151.2 (Cq), 146.2 (2Cq), 137.3 (Cq), 137.2 (Cq), 136.88 (Cq), 136.85 (Cq), 134.1 (Cq), 134.0 (Cq), 130.2 (Cq), 129.8 (Cq), 129.7 (CH), 129.49 (CH), 129.45 (CH), 129.1 (2CH), 129.0 (2CH), 128.83 (2CH), 128.82 (2CH), 128.81 (4CH), 127.99 (2CH), 127.94 (2CH), 127.84 (CH), 127.79 (CH), 127.67 (CH), 127.64 (CH), 127.63 (CH), 125.1 (Cq), 122.3 (Cq), 121.7 (CH), 118.8 (CH), 118.7 (CH), 114.5 (CH), 113.5 (CH), 112.1 (CH), 111.8 (CH), 111.7 (CH), 111.6 (CH), 108.6 (CH), 66.4 (CH), 66.1 (CH), 55.5 (CH_3), 55.4 (CH_3), 55.2 (CH_3), 55.1 (CH_3), 52.4 (CH_2), 52.2 (CH_2), 47.70 (CH), 47.66 (CH), 46.19 (CH_2), 46.16 (CH_2), 45.2 (CH_2), 45.0 (CH_2), 42.93 (CH), 42.88

(CH), 38.7 (CH), 38.1 (CH), 32.1 (CH_2), 32.0 (CH), 31.7 (CH), 29.5 (CH_2), 25.1 (CH_2). **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_4$ $[M+H]^+$ 611.2904, found 611.2895.

(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-6-(3-methoxyphenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-5-methoxy-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10k'A was isolated following the **GP-2** using **9k** as reagent (61.1 mg, 0.20 mmol). Yield **17%** (10.3 mg, 0.017 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.43 (m, 4H), 7.43 – 7.17 (m, 7H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.87 – 6.72 (m, 4H), 6.39 (d, *J* = 2.6 Hz, 1H), 5.53 (d, *J* = 15.1 Hz, 1H), 4.72 – 4.55 (m, 3H), 4.29 (brs, 1H), 4.01 – 3.63 (m, 9H), 3.65 – 3.45 (m, 3H), 2.72 (d, *J* = 6.7 Hz, 1H), 2.47 (q, *J* = 7.5 Hz, 1H), 2.19 – 1.99 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6 (Cq), 170.0 (Cq), 159.7 (Cq), 158.5 (Cq), 151.3 (Cq), 146.1 (Cq), 137.5 (Cq), 137.3 (Cq), 135.8 (Cq), 130.3 (Cq), 129.7 (CH), 129.5 (CH), 128.92 (2CH), 128.86 (2CH), 128.8 (2CH), 128.1 (2CH), 127.7 (CH), 127.6 (CH), 125.2 (Cq), 118.6 (CH), 113.6 (CH), 113.2 (CH), 112.5 (CH), 111.3 (CH), 69.2 (CH), 55.3 (CH_3), 55.2 (CH_3) , 52.0 (CH_2), 48.2 (CH), 46.2 (CH_2), 45.3 (CH_2), 43.0 (CH), 38.7 (CH), 31.9 (CH_2), 30.6 (CH), 29.7 (CH_2). **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_4$ $[M+H]^+$ 611.2904, found 611.2908.

(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-6-(3-methoxyphenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-7-methoxy-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10k'B was isolated following the **GP-2** using **9k** as reagent (61.1 mg, 0.20 mmol). Yield **18%** (10.9 mg, 0.018 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.30 (m, 8H), 7.27 – 7.12 (m, 4H), 6.84 – 6.72 (m, 4H), 6.55 (d, *J* = 7.7 Hz, 1H), 5.52 (d, *J* = 15.2 Hz, 1H), 4.74 – 4.52 (m, 3H), 4.36 (brs, 1H), 3.94 (d, *J* = 19.2 Hz, 1H), 3.89 – 3.62 (m, 8H), 3.59 – 3.50 (m, 2H), 3.42 (dd, *J* = 22.9, 3.5 Hz, 1H), 2.72 (d, *J* = 6.5 Hz, 1H), 2.51 (q, *J* = 7.3 Hz, 1H), 2.13 – 1.94 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.7 (Cq), 170.1 (Cq), 159.7 (Cq), 156.9 (Cq), 151.0 (Cq), 146.2 (Cq), 137.6 (Cq), 137.4 (Cq), 135.7 (Cq), 130.0 (Cq), 129.5 (CH), 128.9 (2CH), 128.8 (2CH), 128.7 (2CH), 128.1 (2CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 122.4 (Cq), 120.9 (CH), 118.6 (CH), 112.5 (CH), 111.4 (CH), 108.2 (CH), 69.2 (CH), 55.3 (CH_3), 55.2 (CH_3), 52.2 (CH_2), 48.2 (CH), 46.2 (CH_2), 45.2 (CH_2), 43.0 (CH), 38.4 (CH), 31.9 (CH_2), 30.6 (CH), 25.2 (CH_2). **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_4$ $[M+H]^+$ 611.2904, found 611.2910.

R)-5-((1S,2S,5R,6S)-6-(benzo[d][1,3]dioxol-5-yl)-3-benzyl-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-7-benzyl-7,8-dihydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2-f]isoindol-6(9H)-one 10l was isolated following the **GP-2** using **9l** as reagent (63.7 mg, 0.2 mmol). Yield **26%** (16.7 mg, 0.026 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.18 (m, 11H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.59 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.51 (s, 1H), 5.96 – 5.92 (m, 2H), 5.90 (s, 2H), 5.28 (d, *J* = 14.8 Hz, 1H), 4.81 (d, *J* = 15.0 Hz, 1H), 4.47 (d, *J* = 15.0 Hz, 1H), 4.15 – 4.09 (m, 1H), 4.03 – 3.65 (m, 5H), 3.50 (td, *J* = 22.7, 21.9, 3.1 Hz, 1H), 3.34 – 3.25 (m, 1H), 2.63 (q, *J* = 7.4 Hz, 1H), 2.20 – 2.14 (m, 1H), 2.03 – 1.85 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.0 (Cq), 170.0 (Cq), 151.0 (Cq), 147.8 (Cq), 147.1 (Cq), 146.8 (Cq), 145.8 (Cq), 138.6 (Cq), 137.2 (Cq), 136.8 (Cq), 130.5 (Cq), 129.0 (2CH), 128.8 (2CH), 128.8 (2CH), 128.0 (2CH), 127.8 (CH), 127.7 (CH), 126.5 (Cq), 126.0 (Cq), 119.3 (CH), 109.2 (CH), 108.4 (CH), 108.1 (CH), 106.9 (CH), 101.3 (CH_2), 100.9 (CH_2), 66.3 (CH), 52.1 (CH_2), 48.0 (CH), 46.2 (CH_2), 45.1 (CH_2), 42.9 (CH), 38.5 (CH_2), 32.3 (CH_2), 31.5 (CH), 30.5 (CH_2). **ESI-HRMS** calcd for $C_{40}H_{34}N_2NaO_6$ $[M+Na]^+$ 661.2309, found 661.2313.

(S)-5-((1S,2S,5R,6S)-6-(benzo[d][1,3]dioxol-5-yl)-3-benzyl-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-7-benzyl-7,8-dihydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2-f]isoindol-6(9H)-one 10l' was isolated following the **GP-2** using **9l** as reagent (63.7 mg, 0.206 mmol). Yield **35%** (22.1 mg, 0.035 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 8H), 7.25 – 7.21 (m, 2H), 6.74 – 6.67 (m, 2H), 6.66 – 6.61 (m, 2H), 6.31 (s, 1H), 5.95 – 5.88 (m, 4H), 5.48 (d, *J* = 15.1 Hz, 1H), 4.68 – 4.56 (m, 2H), 4.53 (d, *J* = 15.4 Hz, 1H), 4.21 (brs, 1H), 3.87 (d, *J* = 19.1 Hz, 1H), 3.75 – 3.62 (m, 2H), 3.53 – 3.39 (m, 3H), 2.60 (d, *J* = 7.7 Hz, 1H), 2.40 (q, *J* = 7.6 Hz, 1H), 2.00 (ddt, *J* = 14.1, 8.4, 4.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.5 (Cq), 169.9 (Cq), 150.7 (Cq), 147.8 (Cq), 146.9 (Cq), 146.9 (Cq), 145.9 (Cq), 138.5 (Cq), 137.5 (Cq), 137.3 (Cq), 130.5 (Cq), 129.0 (2CH), 128.8 (2CH), 128.7 (2CH), 128.2 (2CH), 127.8 (CH), 127.6 (CH), 127.5 (Cq), 126.4 (Cq), 119.3 (CH), 108.4 (CH), 108.4 (CH), 108.1 (CH), 106.9 (CH), 101.3 (CH_2), 100.9 (CH_2), 68.9 (CH), 51.9 (CH_2), 48.5 (CH), 46.2 (CH_2), 45.2 (CH_2), 42.9 (CH), 38.5 (CH), 32.2 (CH_2), 30.7 (CH_2), 30.3 (CH). **ESI-HRMS** calcd for $C_{40}H_{34}N_2NaO_6$ $[M+Na]^+$ 661.2309, found 661.2301.

(R)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-5-deutero-6-(4-chlorophenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10m was isolated following the **GP-2** using **9m** as reagent (63.6 mg, 0.2 mmol). Yield **20%** (12.4 mg, 0.019 mmol).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.17 (m, 15H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 5.32 (d, *J* = 14.2 Hz, 1H), 4.84 (d, *J* = 14.9 Hz, 1H), 4.50 (d, *J* = 15.0 Hz, 1H), 4.23 (brs, 1H), 4.05 – 3.94 (m, 2H), 3.90 (d, *J* = 2.4 Hz, 1H), 3.87 – 3.74 (m, 2H), 3.57 (dd, *J* = 22.2, 2.9 Hz, 1H), 3.37 (dd, *J* = 9.0, 3.9 Hz, 1H), 2.67 – 2.56 (m, 1H), 2.07 (ddt, *J* = 13.0, 9.0, 4.1 Hz, 1H), 2.01 – 1.91 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.9 (Cq), 169.8 (Cq), 150.4 (Cq), 142.6 (Cq), 137.0 (Cq), 136.5 (Cq), 135.2 (Cq), 133.3 (Cq), 132.0 (Cq), 130.7 (Cq), 130.4 (Cq), 129.0 (2CH), 128.9 (2CH), 128.9 (CH), 128.9 (2CH), 128.6 (2CH), 128.3 (CH), 128.0 (CH), 128.0 (2CH), 127.8 (CH), 127.7 (2CH), 127.3 (CH), 66.1 (CH), 52.2 (CH_2), 47.6 (CH, residual peak), 46.3 (CH_2), 45.2 (CH_2), 42.2 (CH), 38.0 (CH), 31.8 (CH_2), 31.4 (CH), 30.1 (CH_2). **ESI-HRMS** calcd for $C_{38}H_{32}Cl_2N_2NaO_2$ $[M+Na]^+$ 642.1796, found 642.1802.

(S)-2-benzyl-9-((1S,2S,5R,6S)-3-benzyl-5-deutero-6-(4-chlorophenyl)-4-oxo-3-azabicyclo[3.2.0]heptan-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-benzo[f]isoindol-1-one 10m' was isolated following the **GP-2** using **9m** as reagent (63.6 mg, 0.2 mmol). Yield **17%** (11.1 mg, 0.017 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.00 (m, 16H), 6.83 (d, *J* = 8.3 Hz, 1H), 5.48 (d, *J* = 15.2 Hz, 1H), 4.61 (s, 2H), 4.50 (d, *J* = 14.8 Hz, 1H), 4.28 (s, 1H), 3.89 (d, *J* = 19.2 Hz, 1H), 3.81 – 3.65 (m, 2H), 3.58 – 3.43 (m, 3H), 2.46 – 2.36 (m, 1H), 2.14 – 1.90 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.5 (Cq), 169.7 (Cq), 150.3 (Cq), 142.5 (Cq), 137.3 (Cq), 137.0 (Cq), 135.2 (Cq), 132.9 (Cq), 132.8 (Cq), 132.0 (Cq), 130.5 (Cq), 130.2 (CH), 129.0 (2CH), 128.9 (2CH), 128.8 (CH), 128.7 (2CH), 128.6 (2CH), 128.2 (2CH), 127.9 (CH), 127.7 (2CH), 127.7 (CH), 127.6 (CH), 68.9 (CH), 51.9 (CH_2), 48.3 (CH, residual peak), 46.2 (CH_2), 45.4 (CH_2), 42.2 (CH), 38.2 (CH), 31.5 (CH_2), 30.3 (CH), 30.3 (CH_2). **ESI-HRMS** calcd for $C_{38}H_{32}Cl_2N_2NaO_2$ $[M+Na]^+$ 642.1796, found 642.1805.

(1R,2S,8R,12R,13R)-4,10-dibenzyl-2,8-dimethyl-11-methylene-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12a was isolated via recrystallization from the **12a/12a'** mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* =

7.5, 1.9 Hz, 2H), 7.43 – 7.35 (m, 10H), 7.21 – 7.15 (m, 2H), 7.08 (q, J = 7.4 Hz, 4H), 7.03 – 6.98 (m, 2H), 6.12 (s, H_5), 5.65 (d, J = 14.0 Hz, $H_{10'}$), 5.18 (d, J = 14.0 Hz, $H_{4'}$), 4.82 (s, $H_{11'}$), 4.65 (s, H_1), 4.27 (d, J = 14.0 Hz, $H_{4'}$), 4.22 (d, J = 14.0 Hz, $H_{10'}$), 3.43 (s, H_{12}), 3.26 (s, H_{13}), 2.79 (d, J = 12.7 Hz, H_7), 2.21 (d, J = 12.8 Hz, H_7), 1.41 (s, $3H_{2'}$), 0.88 (s, $3H_{8'}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.6 (C_9), 172.9 (C_3), 146.6 (C_{11}), 145.2 (Cq Ar), 136.1 (C_3), 136.0 (Cq), 135.7 (Cq), 130.0 (2CH), 129.7 (2CH), 129.3 (2CH), 128.9 (C_5), 128.7 (2CH), 128.7 (2CH), 128.25 (4CH), 128.20 (2CH), 128.1 (2CH), 127.2 (CH), 126.2 (CH), 118.2 (C_6), 115.7 ($C_{11'}$), 71.0 (C_1), 56.2 (C_{12}), 54.6 (C_2), 53.9 ($C_{10'}$), 50.1 ($C_{4'}$), 49.0 (C_7), 46.4 (C_{13}), 46.2 (C_8), 26.5 ($C_{8'}$), 24.2 ($C_{2'}$). **ESI-MS** calcd for $C_{40}H_{39}N_2O_2$ $[M+H]^+$ 579.30, found 579.26. **ESI-HRMS** calcd for $C_{40}H_{39}N_2O_2$ $[M+H]^+$ 579.3006, found 579.3011.

(1R,2S,8R,12R,13R)-4,10-dibenzyl-2,8-dimethyl-11-methylene-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione compound with **(1S,2S,8S,12S,13R)-4,10-dibenzyl-2,8-dimethyl-11-methylene-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12a/12a'** mixture was isolated following the **GP-2** using **11a** as reagent (28.9 mg, 0.1 mmol). Yield **64%** (18.5 mg, 0.032 mmol, dr 55:45). **^{1}H NMR** (400 MHz,$_3$ $CDCl_3$) δ 7.54 – 6.90 (m, $18H_A$, $18H_B$), 6.73 – 6.42 (m, $2H_A$, $2H_B$) 6.31 (s, $1H_A$), 6.12 (s, $1H_B$), 5.65 (d, J = 14.0 Hz, $1H_B$), 5.39 (d, J = 13.8 Hz, $1H_A$), 5.32 (d, J = 14.2 Hz, $1H_A$), 5.18 (d, J = 14.0 Hz, $1H_B$), 5.03 (d, J = 2.3 Hz, $1H_A$), 4.82 (s, $1H_B$), 4.78 (d, J = 2.0 Hz, $1H_A$), 4.65 (s, $1H_B$), 4.49 – 4.38 (m, $1H_A$, $1H_B$), 4.28 (d, J = 14.1 Hz, $1H_A$, $1H_B$), 4.22 (d, J = 14.0 Hz, $1H_B$), 3.98 (s, $1H_A$), 3.51 (d, J = 14.2 Hz, $1H_a$), 3.47 – 3.40 (m, $1H_A$, $1H_B$), 3.26 (s, $1H_B$), 2.79 (d, J = 12.7 Hz, 1 H_B), 2.66 (d, J = 12.7 Hz, 1H), 2.46 (d, J = 12.7 Hz, 1H), 2.21 (d, J = 12.7 Hz, $1H_B$), 1.41 (s, $3H_B$), 1.21 (s, $3H_A$), 0.88 (s, $3H_B$), 0.86 (s, $3H_A$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.6 (Cq), 174.1 (Cq), 173.7 (Cq), 172.9 (Cq), 146.7 (Cq), 146.6 (Cq), 145.2 (Cq), 144.9 (Cq), 136.9 (Cq), 136.09 (Cq), 136.08 (Cq), 136.0 (Cq), 135.9 (Cq), 135.7 (Cq), 130.0 (2CH), 129.9 (2CH), 129.7 (2CH), 129.32 (2CH), 129.28 (2CH), 129.0 (2CH), 128.9 (CH), 128.8 (4CH), 128.72 (2CH), 128.67 (2CH), 128.5 (2CH), 128.24 (brs, 6CH), 128.20 (2CH), 128.19 (CH), 128.11 (2CH), 128.07 (2CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 126.3 (CH), 126.2 (CH), 121.0 (CH_2), 119.0 (Cq), 118.2 (Cq), 115.7 (CH_2), 72.1 (CH), 71.0 (CH), 57.9 (CH), 56.2 (CH), 54.6 (Cq), 53.9 (CH_2), 50.9 (CH_2), 50.8 (CH_2), 50.2 (CH_2), 50.1 (CH_2), 50.0 (Cq), 49.0 (CH_2), 48.9 (Cq), 47.4 (CH), 46.4 (CH), 46.2

(Cq), 26.7 (CH_3), 26.5 (CH_3), 24.2 (CH_3), 21.6 (CH_3). **ESI-MS** calcd for $C_{40}H_{39}N_2O_2$ $[M+H]^+$ 579.30, found 579.26.

(1R,2S,8R,12R,13R)-4,10-dibenzyl-11-methylene-12,13-diphenyl-2,8-dipropyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione compound with **(1S,2S,8S,12S,13R)-4,10-dibenzyl-11-methylene-12,13-diphenyl-2,8-dipropyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12b/12b'** mixture was isolated following the **GP-2** using **11b** as reagent (65.5 mg, 0.206 mmol). Yield **54%** (35.1 mg, 0.055 mmol, dr 61:39). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 6.80 (m, $20H_A$, $18H_B$), 6.64 – 6.39 (m, $2H_B$) 6.24 (s, $1H_A$), 6.03 (s, $1H_B$), 5.43 (d, J = 13.8 Hz, $1H_B$), 5.35 (d, J = 13.7 Hz, $1H_A$), 5.29 (d, J = 13.9 Hz, $1H_A$), 5.18 (d, J = 13.9 Hz, $1H_B$), 4.96 (s, $1H_B$), 4.91 (d, J = 6.5 Hz, $1H_A$, $1H_B$), 4.86 (d, J = 1.5 Hz, $1H_B$), 4.74 (s, $1H_B$), 4.43 (s, $1H_B$), 4.28 – 4.20 (m, $1H_A$, $1H_B$), 4.11 (d, J = 13.8 Hz, $1H_A$), 3.98 (s, $1H_A$), 3.51 – 3.43 (m, $1H_A$, $1H_B$), 3.32 (s, $1H_A$), 3.19 (s, $1H_B$), 2.60 – 2.39 (m, $2H_A$, $2H_B$), 2.09 – 1.87 (m, 3H), 1.80 – 1.12 (m, 10H), 1.05 – 0.93 (m, 3H), 0.92 – 0.80 (m, $6H_B$), 0.57 – 0.45 (m, $6H_A$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (Cq), 174.5 (Cq), 173.7 (Cq), 172.7 (Cq), 146.7 (Cq), 146.4 (Cq), 144.9 (Cq), 144.7 (Cq), 136.55 (Cq), 136.53 (Cq), 136.4 (Cq), 136.12 (Cq), 136.07 (Cq), 135.9 (Cq), 129.9 (2CH), 129.74 (2CH), 129.72 (2CH), 129.6 (2CH), 129.4 (2CH), 129.3 (2CH), 128.9, 128.8 (2CH), 128.7 (4CH), 128.6 (2CH), 128.23 (10CH), 128.16 (2CH), 128.1 (2CH), 127.93 (2CH), 127.89 (CH), 127.23 (CH), 127.16 (CH), 127.0 (CH), 126.04 (CH), 126.02 (CH), 119.17 (Cq), 119.15 (CH_2), 118.6 (Cq), 114.7 (CH_2), 65.8 (CH), 65.1 (CH), 56.8 (CH_2), 55.6 (CH), 54.4 (CH), 52.4 (CH_2), 51.8 (CH_2), 51.3 (CH_2), 50.9 (CH_2), 50.2 (CH_2), 50.1 (CH_2), 49.0 (CH), 48.4 (CH_2), 47.6 (CH), 47.0 (CH_2), 43.9 (CH_2), 39.3 (CH_2), 38.7 (CH_2), 38.6 (CH_2), 37.1 (CH_2), 19.9 (CH_2), 19.1 (CH_2), 16.9 (CH_2), 15.6 (CH_2), 14.93 (CH_3), 14.86 (CH_3), 14.5 (CH_3), 14.4 (CH_3). **ESI-HRMS** calcd for $C_{44}H_{46}N_2NaO_2$ $[M+Na]^+$ 657.3451, found 657.3458.

(1S,2R,8S,12S,13R)-4,10-dibenzyl-11-methylene-12,13-diphenyl-2,8-bis(phenylethynyl)-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12c was isolated following the **GP-2** using **11c** as reagent (60.5 mg, 0.16 mmol). Yield **34%** (20.8 mg, 0.028 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 – 7.54 (m, 2H), 7.48 – 6.96 (m, 26H), 6.84 – 6.77 (m, 2H), 6.23 (s, 1H), 5.94 (d, J = 14.1 Hz, 1H), 5.29 (s, 1H), 5.08 (d, J = 14.2 Hz, 1H), 5.02 (d, J = 14.1 Hz, 1H), 4.96 (s, 1H), 4.49 (s, 1H), 4.39 (d, J = 14.3

Hz, 1H), 3.78 (s, 1H), 3.75 (s, 1H), 3.46 (d, J = 13.0 Hz, 1H), 2.90 (d, J = 13.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1 (Cq), 168.0 (Cq), 144.7 (Cq), 142.4 (Cq), 135.7 (Cq), 135.5 (Cq), 134.9 (Cq), 131.7 (CH), 131.6 (CH), 130.8 (CH), 130.2 (CH), 129.5 (CH), 129.2 (CH), 128.8 (CH), 128.74 (CH), 128.71 (CH), 128.68 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.94 (CH), 127.88 (CH), 127.8 (CH), 127.4 (CH), 126.6 (CH), 123.0 (Cq), 122.4 (Cq), 117.4 (CH_2), 115.7 (Cq), 90.5 (Cq), 89.8 (Cq), 89.5 (Cq), 87.7 (Cq), 67.1 (CH), 56.8 (Cq), 55.5 (CH), 50.6 (Cq), 50.3 (CH_2), 50.2 (CH_2), 48.8 (CH_2), 45.8 (CH). **ESI-HRMS** calcd for $C_{54}H_{43}N_2O_2$ $[M+H]^+$ 751.3319, found 751.3326.

(1S,2S,8S,12S,13R)-4,10-dibenzyl-12,13-bis(4-chlorophenyl)-2,8-dimethyl-11-methylene-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione compound with (1R,2S,8R,12S,13R)-4,10-dibenzyl-12,13-bis(4-chlorophenyl)-2,8-dimethyl-11-methylene-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12d/12d' mixture was isolated following the **GP-2** using $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ instead of $Ir(ppy)_3$ and **11d** as reagent (65.3 mg, 0.202 mmol, dr 50:50). Yield **31%** (20.5 mg, 0.029 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.13 (m, $14H_A$, $14H_B$), 7.00 (d, J = 8.5 Hz, $2H_B$), 6.96 (d, J = 8.5 Hz, $2H_A$), 6.86 (d, J = 8.5 Hz, $2H_B$), 6.79 (d, J = 8.5 Hz, $2H_A$), 6.28 (s, $1H_A$), 6.09 (s, $1H_B$), 5.61 (d, J = 13.9 Hz, $1H_B$), 5.40 (d, J = 13.8 Hz, $1H_A$), 5.30 (d, J = 14.1 Hz, $1H_A$), 5.20 (d, J = 14.0 Hz, $1H_B$), 5.02 (d, J = 2.1 Hz, $1H_A$), 4.81 (s, $1H_B$), 4.74 (d, J = 2.0 Hz, $1H_A$), 4.63 (s, $1H_B$), 4.40 (d, J = 10.6 Hz, $1H_A$, $1H_B$), 4.20 – 4.09 (m, $1H_A$, $2H_B$), 3.90 (s, $1H_A$), 3.47 (d, J = 14.1 Hz, $1H_A$), 3.38 (s, $1H_B$), 3.33 (s, $1H_A$), 3.19 (s, $1H_B$), 2.72 (d, J = 12.8 Hz, $1H_B$), 2.63 (d, J = 12.8 Hz, $1H_A$), 2.39 (d, J = 12.8 Hz, $1H_A$), 2.17 (d, J = 12.8 Hz, $1H_B$), 1.38 (s, $3H_B$), 1.16 (s, $3H_A$), 0.83 (d, J = 2.0 Hz, $3H_A$, $3H_B$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.1 (Cq), 173.7 (Cq), 173.2 (Cq), 172.4 (Cq), 146.3 (Cq), 145.2 (Cq), 144.5 (Cq), 143.6 (Cq), 136.7 (Cq), 136.0 (Cq), 135.82 (Cq), 135.76 (Cq), 134.3 (Cq), 134.0 (Cq), 133.18 (Cq), 133.14 (Cq), 132.2 (Cq), 132.1 (Cq), 130.7 (2CH), 130.6 (2CH), 130.0 (2CH), 129.8 (2CH), 129.6 (2CH), 129.2 (CH), 129.1 (2CH), 128.9 (2CH), 128.8 (4CH), 128.8 (2CH), 128.7 (CH), 128.6 (2CH), 128.4 (CH), 128.37 (CH), 128.33 (2CH), 128.2 (2CH), 128.0 (CH), 127.8 (CH), 127.73 (CH), 127.66 (2CH), 126.5 (CH), 123.0 (Cq), 121.4 (CH_2), 117.8 (Cq), 116.0 (CH_2), 71.8 (CH), 71.0 (CH), 57.1 (CH), 55.6 (CH), 54.6 (Cq), 54.0 (CH_2), 50.9 (CH_2), 50.6 (CH_2), 50.3 (CH_2), 50.2 (CH_2), 50.0 (Cq), 48.8 (Cq), 48.7 (CH_2), 46.8 (CH), 46.1 (Cq), 45.8 (CH), 26.8 (CH_3), 26.5 (CH_3), 24.2 (CH_3), 21.6 (CH_3). **ESI-HRMS** calcd for $C_{40}H_{36}Cl_2N_2NaO_2$ $[M+Na]^+$ 669.2046, found 669.2039.

(1S,2S,8S,12S,13R)-4,10-dibenzyl-12,13-bis(4-methoxyphenyl)-2,8-dimethyl-11-methylene-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione compound with (1R,2S,8R,12S,13R)-4,10-dibenzyl-12,13-bis(4-methoxyphenyl)-2,8-dimethyl-11-methylene-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12e/12e' mixture was isolated following the **GP-2** using **11e** as reagent (65.2 mg, 0.204 mmol). Yield **41%** (27.0 mg, 0.041 mmol, dr 53:47). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.28 (m, $12H_A$, $12H_B$), 6.88 (d, J = 8.7 Hz, $2H_B$), 6.81 (d, J = 8.7 Hz, $2H_A$), 6.68 – 6.43 (m, $4H_A$, $4H_B$), 6.26 (s, $1H_A$), 6.06 (s, $1H_B$), 5.61 (d, J = 14.0 Hz, $1H_B$), 5.36 (d, J = 13.8 Hz, $1H_A$), 5.28 (d, J = 14.3 Hz, $1H_A$), 5.16 (d, J = 14.0 Hz, $1H_B$), 4.99 (d, J = 2.2 Hz, $1H_A$), 4.83 – 4.72 (m, $1H_A$, $1H_B$), 4.61 (s, $1H_B$), 4.39 (s, $1H_A$, $1H_B$), 4.29 – 4.12 (m, $2H_A$, $1H_B$), 3.90 (d, J = 6.3 Hz, $1H_A$), 3.78 – 3.68 (m, $6H_A$, $6H_B$), 3.47 (d, J = 14.2 Hz, $1H_A$), 3.35 (d, J = 6.7 Hz, $1H_A$, $1H_B$), 3.17 (s, $1H_B$), 2.74 (d, J = 12.7 Hz, $1H_B$), 2.61 (d, J = 12.7 Hz, $1H_A$), 2.40 (d, J = 12.6 Hz, $1H_A$), 2.16 (d, J = 12.7 Hz, $1H_B$), 1.37 (s, $3H_B$), 1.17 (s, $3H_A$), 0.85 (s, $3H_B$), 0.83 (s, $3H_A$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.7 (Cq), 174.2 (Cq), 173.7 (Cq), 172.9 (Cq), 158.73 (Cq), 158.66 (Cq), 158.0 (Cq), 157.9 (Cq), 147.1 (Cq), 145.2 (Cq), 139.1 (Cq), 137.6 (Cq), 137.0 (Cq), 136.2 (Cq), 136.1 (Cq), 136.0 (Cq), 130.34 (2CH), 130.32 (2CH), 130.0 (3CH), 129.9 (2CH), 129.7 (2CH), 129.3 (2CH), 129.2 (2CH), 129.0 (2CH), 128.8 (2CH), 128.72 (4CH), 128.67 (2CH), 128.5 (3CH), 128.1 (CH), 128.04 (2CH), 127.97 (Cq), 127.7 (CH), 127.6 (Cq), 127.2 (CH), 120.8 (CH_2), 119.4 (Cq), 118.6 (Cq), 115.4 (CH_2), 113.5 (2CH), 113.4 (2CH), 72.0 (CH), 71.0 (CH), 57.1 (CH), 55.4 (CH_2), 55.20 (CH_3), 55.19 (CH_3), 55.18 (CH_3), 55.1 (CH_3), 54.7 (Cq), 53.9 (CH_2), 50.8 ($2CH_2$), 50.2 (CH_2), 50.14 (CH_2), 50.14 (Cq), 49.2 (Cq), 48.9 (CH_2), 46.6 (CH), 46.4 (Cq), 45.6 (CH), 26.8 (CH_3), 26.6 (CH_3), 24.2 (CH_3), 21.6 (CH_3). **ESI-HRMS** calcd for $C_{42}H_{43}N_2O_4$ $[M+H]^+$ 639.3217, found 639.3211.

(1S,2S,8S,12S,13R)-4,10-dibenzyl-12,13-bis(4-butylphenyl)-2,8-dimethyl-11-methylene-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12f was isolated following the **GP-2** using **11f** as reagent (66.3 mg, 0.20 mmol). Yield **22%** (14.5 mg, 0.022 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.32 (m, 12H), 7.01 – 6.37 (m, 6H), 6.05 (s, H_5), 5.61 (d, J = 14.0 Hz, $H_{10'}$), 5.12 (d, J = 14.0 Hz, $H_{4'}$), 4.77 (s, $H_{11'}$), 4.60 (s, H_1), 4.40 – 4.33 (m, $H_{11'}$), 4.27 (d, J = 14.1 Hz, $H_{4'}$), 4.20 (d, J = 14.0 Hz, $H_{10'}$), 3.36 (s, H_{12}), 3.19 (s, H_{13}), 2.75 (d, J = 12.7 Hz, H_7), 2.60 – 2.42 (m, 4H), 2.16 (d, J = 12.8 Hz, H_7), 1.52 (tdd, J = 15.3, 11.0, 7.5 Hz, 4H), 1.38 – 1.25 (m, 4H + $3H_{2'}$), 1.00 – 0.87 (m, 6H), 0.84 (s, $3H_{8'}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8 (C_9), 173.1 (C_3), 146.8 (C_{11}),

142.5 (Cq), 141.8 (Cq), 140.7 (Cq), 136.1 (Cq), 136.0 (Cq), 132.9 (Cq), 130.0 (2CH), 129.7 (2CH), 129.1 (2CH), 128.7 (2CH), 128.67 (C_5), 128.6 (2CH), 128.21 (2CH), 128.15 (brs, 4CH) 128.0 (2CH), 118.5 (C_6), 115.5 ($C_{11'}$), 70.9 (C_1), 55.8 (C_{12}), 54.6 (Cq), 53.8 (C_{10}), 50.1 ($C_{4'}$), 49.0 (C_7), 46.3 (Cq), 46.1 (C_{13}), 35.11 (CH_2), 35.09 (CH_2), 33.5 (CH_2), 33.4 (CH_2), 26.6 ($C_{8'}$), 24.2 ($C_{2'}$), 22.39 (CH_2), 22.37 (CH_2), 14.1 (CH_3), 14.0 (CH_3). **ESI-HRMS** calcd for $C_{49}H_{55}N_2O_2$ $[M+H]^+$ 691.4258, found 691.4265.

(1R,2S,8R,12S,13R)-4,10-dibenzyl-12,13-bis(4-butylphenyl)-2,8-dimethyl-11-methylene-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12f' was isolated following the **GP-2** using **11f** as reagent (66.3 mg, 0.20 mmol). Yield **20%** (13.5 mg, 0.020 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.31 (m, 12H), 7.03 – 6.72 (m, 6H), 6.27 (s, H_5), 5.36 (d, *J* = 13.8 Hz, $H_{4'}$), 5.30 (d, *J* = 14.3 Hz, $H_{10'}$), 5.01 (d, *J* = 2.2 Hz, $H_{11'}$), 4.79 (d, *J* = 1.9 Hz, $H_{11'}$), 4.41 (s, $H_{1'}$), 4.28 (d, *J* = 13.8 Hz, $H_{4'}$), 3.94 (s, H_{12}), 3.50 (d, *J* = 14.2 Hz, $H_{10'}$), 3.40 (s, H_{13}), 2.63 (d, *J* = 12.7 Hz, H_7), 2.54 (td, *J* = 8.0, 2.8 Hz, 4H), 2.44 (d, *J* = 12.7 Hz, H_7), 1.55 (dtt, *J* = 12.5, 7.8, 3.4 Hz, 4H), 1.44 – 1.24 (m, 4H), 1.21 (s, $3H_{2'}$), 1.02 – 0.89 (m, 6H), 0.84 (s, $3H_{8'}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3 (Cq), 173.9 (Cq), 145.0 (Cq), 143.9 (Cq), 141.8 (Cq), 140.9 (Cq), 136.9 (Cq), 135.9 (Cq), 133.2 (Cq), 129.9 (2CH), 129.1 (4CH), 129.0 (2CH), 128.7 (4CH), 128.5 (2CH), 128.14 (CH), 128.13 (2CH), 127.7 (CH), 127.1 (C_5), 120.9 ($C_{11'}$), 119.3 (C_6), 72.1 (C_1), 57.5 (C_{12}), 50.9 (C_7), 50.8 ($C_{10'}$), 50.2 ($C_{4'}$), 50.0 (Cq), 49.0 (Cq), 47.0 (C_{13}), 35.2 (CH_2), 35.1 (CH_2), 33.5 ($2CH_2$), 26.7 ($C_{8'}$), 22.40 (CH_2), 22.36 (CH_2), 21.6 ($C_{2'}$), 14.0 ($2CH_3$). **ESI-HRMS** calcd for $C_{49}H_{55}N_2O_2$ $[M+H]^+$ 691.4258, found 691.4254.

di-tert-butyl 3,3'-((1S,2S,8S,12R,13S)-4,10-dibenzyl-2,8-dimethyl-11-methylene-3,9-dioxo-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-12,13-diyl)bis(2-methyl-1H-indole-1-carboxylate) 12g was isolated following the **GP-2** using **11g** as reagent (65.0 mg, 0.147 mmol). Yield **31%** (20.6 mg, 0.023 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.19 (m, 12H), 7.13 (d, *J* = 6.9 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 6.16 (s, 1H), 5.66 (d, *J* = 14.3 Hz, 1H), 5.44 (d, *J* = 13.8 Hz, 1H), 4.77 (s, 1H), 4.66 (s, 1H), 4.29 (d, *J* = 14.4 Hz, 1H), 4.21 – 4.08 (m, 2H), 3.84 (s, 1H), 3.72 (s, 1H), 2.93 (d, *J* = 12.5 Hz, 1H), 2.72 (s, 3H), 2.24 (s, 3H), 1.97 (d, *J* = 12.6 Hz, 1H), 1.69 (s, 9H), 1.69 (s, 9H), 1.37 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.1 (Cq), 174.2 (Cq), 150.7 (Cq),

150.4 (Cq), 141.7 (Cq), 136.6 (Cq), 136.2 (Cq), 135.5 (2Cq), 135.4 (Cq), 134.5 (Cq), 130.2 (2CH), 130.1 (2CH), 128.9 (2CH), 128.7 (2CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.53 (Cq), 126.6 (CH), 123.2 (2CH), 122.6 (Cq), 122.5 (CH), 121.0 (Cq), 120.2 (CH), 120.1(CH), 118.3 (CH_2), 116.1 (2Cq), 115.2 (CH), 115.0 (CH), 84.1 (Cq), 83.8 (Cq), 71.3 (CH), 53.4 (CH_2), 52.9 (Cq), 50.9 (CH_2), 49.2 (CH_2), 44.2 (Cq), 44.1 (CH), 38.1 (CH), 28.34 ($3CH_3$), 28.30 ($3CH_3$), 25.1 (CH_3), 24.0 (CH_3), 15.1 (CH_3), 13.8 (CH_3). **ESI-HRMS** calcd for $C_{56}H_{60}N_4NaO_6$ $[M+Na]^+$ 907.4405 found 907.4418.

di-tert-butyl 3,3'-((1R,2S,8R,12R,13S)-4,10-dibenzyl-2,8-dimethyl-11-methylene-3,9-dioxo-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-12,13-diyl)bis(2-methyl-1H-indole-1-carboxylate) 12g' was isolated as a mixture of atropisomers following the **GP-2** using **11g** as reagent (65.0 mg, 0.147 mmol). Yield **12%** (7.7 mg, 0.087 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.4, 3.8 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 2H), 7.46 – 7.33 (m, 8H), 7.21 – 7.13 (m, 2H), 7.10 – 7.03 (m, 2H), 6.79 (d, *J* = 3.5 Hz, 1H), 6.53 (t, *J* = 7.2 Hz, 1H), 6.40 (s, 1H), 6.29 (d, *J* = 7.8 Hz, 1H), 5.64 (d, *J* = 14.5 Hz, 1H), 4.99 – 4.93 (m, 2H), 4.90 – 4.70 (m, 4H), 4.56 (s, 1H), 4.12 (d, *J* = 14.6 Hz, 1H), 2.68 – 2.48 (m, 8H), 1.71 (s, 9H), 1.70 (s, 9H), 1.28 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.9 (Cq), 172.9 (Cq), 150.7 (Cq), 150.5 (Cq), 144.4 (Cq), 136.3 (Cq), 136.1 (Cq), 135.9 (Cq), 135.8 (Cq), 135.5 (Cq), 135.1 (Cq), 134.6 (Cq), 130.4 (2CH), 130.0 (CH), 129.9 (2CH), 128.9 (2CH), 128.8 (CH), 128.6 (2CH), 128.4 (CH), 128.0 (CH), 127.8 (CH), 127.4 (Cq), 127.0 (Cq), 123.3 (CH), 122.43 (CH), 122.41 (CH), 120.8 (Cq), 120.5 (CH), 120.1 (CH_2), 117.6 (Cq), 114.98 (CH), 114.95 (CH), 83.91 (Cq), 83.89 (Cq), 73.4 (CH), 52.0 (CH_2), 51.45 (Cq), 51.43 (CH_2), 51.0 (CH_2), 48.5 (Cq), 48.2 (CH), 43.2 (CH), 28.3 ($3CH_3$), 28.3 ($3CH_3$), 24.6 (CH_3), 20.1 (CH_3), 14.0 (CH_3), 13.6 (CH_3). **ESI-HRMS** calcd for $C_{56}H_{60}N_4NaO_6$ $[M+Na]^+$ 907.4405 found 907.4440.

(1S,2S,8S,12R,13R)-4,10-bis(4-methoxybenzyl)-2,8-dimethyl-11-methylene-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione compound with **(1R,2S,8R,12S,13R)-4,10-bis(4-methoxybenzyl)-2,8-dimethyl-11-methylene-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12h/12h'** mixture was isolated following the **GP-2** using **11h** as reagent (63.8 mg, 0.20 mmol). Yield **39%** (25.2 mg, 0.039 mmol, dr 53:47). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, $4H_A$, $4H_B$), 7.20 – 6.86 (m, $14H_A$, $12H_B$), 6.71 – 6.38 (m, $2H_B$), 6.25 ($1H_A$), 6.07 ($1H_B$), 5.60 (d, *J* =

14.0 Hz, 1H$_B$), 5.34 – 5.24 (m, 2H$_A$), 5.07 (d, *J* = 14.0 Hz, 1H$_B$), 5.00 (d, *J* = 2.1 Hz, 1H$_A$), 4.78 (s, 1H$_A$), 4.75 (d, *J* = 1.9 Hz, 1H$_B$), 4.60 (s, 1H$_B$), 4.41 – 4.38 (m, 1H$_A$, 1H$_B$), 4.27 – 4.15 (m, 1H$_A$, 1H$_B$), 4.11 (d, *J* = 14.0 Hz, 1H$_B$), 3.93 (brs, 1H$_A$), 3.87 – 3.78 (m, 6H$_A$, 6H$_B$), 3.47 – 3.36 (m, 2H$_A$, 1H$_B$), 3.22 (s, 1H$_B$), 2.75 (d, *J* = 12.7 Hz, 1H$_B$), 2.62 (d, *J* = 12.7 Hz, 1H$_A$), 2.42 (d, *J* = 12.7 Hz, 1H$_A$), 2.17 (d, *J* = 12.8 Hz, 1H$_B$), 1.38 (s, 3H$_B$), 1.18 (s, 3H$_A$), 0.85 (s, 3H$_B$), 0.83 (s, 3H$_A$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5 (Cq), 174.0 (Cq), 173.6 (Cq), 172.8 (Cq), 159.5 (Cq), 159.41 (Cq), 159.36 (Cq), 159.2 (Cq), 146.8 (Cq), 146.7 (Cq), 145.3 (Cq), 145.0 (Cq), 136.2 (Cq), 135.8 (Cq), 131.3 (4CH), 131.1 (2CH), 131.0 (2CH), 130.4 (2CH), 129.33 (2CH), 129.29 (2CH), 129.0 (Cq), 128.8 (CH), 128.3 (Cq), 128.2 (6CH), 128.18 (Cq), 128.16 (Cq), 128.1 (4CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 126.3 (CH), 126.2 (CH), 120.9 (CH_2), 118.9 (Cq), 118.1 (Cq), 115.6 (CH_2), 114.1 (2CH), 114.00 (2CH), 113.98 (2CH), 113.8 (2CH), 71.6 (CH), 70.6 (CH), 57.9 (CH), 56.2 (CH), 55.37 (CH_3), 55.35 (CH_3), 55.34 (CH_3), 55.28 (CH_3), 54.6 (Cq), 53.2 (CH_2), 50.8 (CH_2), 50.1 (CH_2), 50.0 (Cq), 49.5 (CH_2), 49.4 (CH_2), 49.0 (CH_2), 48.9 (Cq), 47.4 (CH), 46.4 (CH), 46.2 (Cq), 26.7 (CH_3), 26.5 (CH_3), 24.2 (CH_3), 21.6 (CH_3). **ESI-HRMS** calcd for $C_{42}H_{43}N_2O_4$ $[M+H]^+$ 639.3217, found 639.3215.

(1S,2S,8S,12S,13R)-4,10-bis(4-fluorobenzyl)-2,8-dimethyl-11-methylene-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione compound with **(1R,2S,8R,12S,13R)-4,10-bis(4-fluorobenzyl)-2,8-dimethyl-11-methylene-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12i/12i'** mixture was isolated following the **GP-2** using **11i** as reagent (67.2 mg, 0.22 mmol). Yield **49%** (32.6 mg, 0.053 mmol, dr 48:52). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.31 (m, 4H$_A$, 4H$_B$), 7.20 – 6.88 (m, 14H$_A$, 14H$_B$), 6.24 (s, 1H$_A$), 6.07 (s, 1H$_B$), 5.57 (d, *J* = 14.0 Hz, 1H$_B$), 5.32 (d, *J* = 13.9 Hz, 1H$_A$), 5.24 (d, *J* = 14.2 Hz, 1H$_A$), 5.13 (d, *J* = 14.1 Hz, 1H$_B$), 5.03 (d, *J* = 2.1 Hz, 1H$_A$), 4.82 – 4.75 (m, 1H$_A$, 1H$_B$), 4.60 (s, 1H$_B$), 4.43 – 4.36 (m, 1H$_A$, 1H$_B$), 4.27 – 4.18 (m, 1H$_A$, 1H$_B$), 4.15 (d, *J* = 14.0 Hz, 1H$_B$), 3.95 (s, 1H$_A$), 3.50 – 3.37 (m, 2H$_A$, 1H$_B$), 3.22 (s, 1H$_B$), 2.77 (d, *J* = 12.7 Hz, 1H$_B$), 2.63 (d, *J* = 12.8 Hz, 1H$_A$), 2.45 (d, *J* = 12.7 Hz, 1H$_A$), 2.19 (d, *J* = 12.8 Hz, 1H$_B$), 1.38 (s, 3H$_B$), 1.19 (s, 3H$_A$), 0.85 (s, 3H$_B$), 0.83 (s, 3H$_A$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.6 (Cq), 174.2 (Cq), 173.8 (Cq), 172.9 (Cq), 162.6 (d, *J* = 246.8 Hz, Cq), 162.54 (d, *J* = 246.8 Hz, Cq), 162.51 (d, *J* = 246.7 Hz, Cq) 162.4 (d, *J* = 245.9 Hz, Cq), 146.7 (Cq), 146.6 (Cq), 145.1 (Cq), 144.8 (Cq), 135.9 (Cq), 135.6 (Cq), 132.7 (d, *J* = 3.3 Hz, Cq), 132.1 (d, *J* = 3.4 Hz, Cq), 131.9 (d, *J* = 3.3 Hz, Cq), 131.8 (d, *J* = 3.3 Hz, Cq), 131.8 (d, *J* = 8.4 Hz, 2CH), 131.6 (d, *J* = 8.2 Hz,

2CH), 131.4 (d, *J* = 8.2 Hz, 2CH), 130.8 (d, *J* = 8.1 Hz, 2CH), 129.2 (2CH), 129.2 (2CH), 128.9 (CH), 128.3 (brs, 6CH), 128.2 (4CH), 128.1 (2CH), 127.3 (CH), 127.3 (CH), 127.2 (CH), 126.4 (CH), 126.4 (CH), 121.2 (CH_2), 119.2 (Cq), 118.4 (Cq), 115.7 (CH_2), 115.6 (d, *J* = 21.6 Hz, 2CH), 115.53 (d, *J* = 21.5 Hz, 2CH), 115.53 (d, *J* = 21.5 Hz, 2CH), 115.4 (d, *J* = 21.5 Hz, 2CH), 72.0 (CH), 71.4 (CH), 57.8 (CH), 56.2 (CH), 54.5 (Cq), 53.4 (CH_2), 50.8 (CH_2), 50.1 (CH_2), 50.0 (Cq), 49.5 (CH_2), 49.5 (CH_2), 48.93 (Cq), 48.90 (CH_2), 47.3 (CH), 46.4 (CH), 46.2 (Cq), 26.7 (CH_3), 26.5 (CH_3), 24.2 (CH_3), 21.6 (CH_3). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -113.6 (tt, *J* = 8.7, 5.3 Hz), -113.7 – -113.8 (m), -114.3 (tt, *J* = 8.7, 5.4 Hz). **ESI-HRMS** calcd for $C_{40}H_{37}F_2N_2O_2$ $[M+H]^+$ 615.2818, found 615.2823.

2,2'-((1S,2S,8S,12S,13R)-2,8-dimethyl-11-methylene-3,9-dioxo-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-4,10-diyl)diacetonitrile 12j was isolated with traces of **10j'** following the **GP-2** using **11j** as reagent (42.0 mg, 0.18 mmol). Yield **35%** (14.7 mg, 0.062 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.15 (m, 8H), 6.91 (d, *J* = 6.5 Hz, 2H), 6.24 (s, 1H), 4.93 (s, 1H), 4.82 (s, 1H), 4.64 (d, *J* = 17.3 Hz, 1H), 4.59 (d, *J* = 16.8 Hz, 1H), 4.47 (s, 1H), 4.40 (d, *J* = 17.3 Hz, 1H), 4.27 (d, *J* = 16.7 Hz, 1H), 3.62 (s, 1H), 3.26 (s, 1H), 2.86 (d, *J* = 13.0 Hz, 1H), 2.38 (d, *J* = 13.0 Hz, 1H), 1.43 (s, 3H), 0.96 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5 (Cq), 172.3 (Cq), 145.6 (Cq), 144.4 (Cq), 133.7 (Cq), 129.1 (2CH), 128.9 (brs, 4CH), 128.8 (2CH), 127.9 (CH), 127.5 (CH), 127.0 (CH), 119.9 (Cq), 116.9 (CH_2), 114.8 (Cq), 114.2 (Cq), 73.5 (CH), 56.2 (CH), 53.8 (Cq), 48.2 (CH_2), 46.6 (Cq), 46.2 (CH), 40.1 (CH_2), 33.0 (CH_2), 25.8 (CH_3), 22.6 (CH_3). **ESI-HRMS** calcd for $C_{30}H_{28}N_4NaO_2$ $[M+Na]^+$ 499.2104, found 499.2098.

2,2'-((1R,2S,8R,12R,13R)-2,8-dimethyl-11-methylene-3,9-dioxo-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-4,10-diyl)diacetonitrile 12j' was isolated following the **GP-2** using **11j** as reagent (42.0 mg, 0.18 mmol). Yield **18%** (7.7 mg, 0.016 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.5 – 7.1 (m, 10H), 6.15 (s, 1H), 5.31 (d, *J* = 2.0 Hz, 1H), 5.05 (d, *J* = 2.1 Hz, 1H), 4.72 (d, *J* = 17.3 Hz, 1H), 4.63 (d, *J* = 16.8 Hz, 1H), 4.42 (s, 1H), 4.38 (d, *J* = 17.3 Hz, 1H), 4.09 (s, 1H), 3.90 (d, *J* = 16.8 Hz, 1H), 3.60 (s, 1H), 2.73 (d, *J* = 12.9 Hz, 1H), 2.61 (d, *J* = 12.9 Hz, 1H), 1.27 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7 (Cq), 174.0 (Cq), 145.8 (Cq), 143.5 (Cq), 134.5 (Cq), 129.0 (2CH), 128.8 (brs,4CH), 128.7 (2CH), 127.9 (CH), 127.0 (CH), 125.3 (CH), 122.7 (CH_2), 121.6 (Cq), 114.8 (Cq), 114.2 (Cq), 74.3 (CH), 58.0 (CH), 50.6 (Cq), 49.9 (CH_2),

48.8 (Cq), 47.3 (CH), 37.5 (CH_2), 33.5 (CH_2), 26.4 (CH), 21.5 (CH). **ESI-HRMS** calcd for $C_{30}H_{28}N_4NaO_2$ $[M+Na]^+$ 499.2104, found 499.2099.

(1S,2S,8S,12S,13R)-4,10-dicyclopropyl-2,8-dimethyl-11-methylene-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12k was isolated following the **GP-2** using **11k** as reagent (47.9 mg, 0.20 mmol). Yield **29%** (13.9 mg, 0.029 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 – 7.10 (m, 6H), 7.05 (dd, *J* = 7.5, 1.9 Hz, 2H), 6.93 – 6.74 (m, 2H), 6.10 (s, 1H), 4.91 (s, 1H), 4.66 (s, 1H), 4.47 (s, 1H), 3.52 (s, 1H), 3.12 (s, 1H), 3.04 – 2.92 (m, 1H), 2.91 – 2.72 (m, 2H), 2.26 (d, *J* = 12.7 Hz, 1H), 1.42 (s, 3H), 1.06 – 0.56 (m, 11H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.8 (Cq), 174.6 (Cq), 147.7 (Cq), 145.7 (Cq), 135.9 (Cq), 130.1 (CH), 129.1 (2CH), 128.4 (brs, 4CH), 128.1 (2CH), 127.2 (CH), 126.5 (CH), 117.0 (Cq), 114.8 (CH_2), 70.8 (CH), 55.5 (CH), 55.4 (CH_2), 49.5 (Cq), 46.6 (Cq), 45.6 (CH), 33.4 (CH), 29.1 (CH), 25.9 (CH_3), 22.6 (CH_3), 12.3 (CH_2), 6.7 (CH_2), 6.4 (CH_2), 4.9 (CH_2). **ESI-HRMS** calcd for $C_{32}H_{34}N_2NaO_2$ $[M+Na]^+$ 501.2512, found 501.2503.

(1R,2S,8R,12R,13R)-4,10-dicyclopropyl-2,8-dimethyl-11-methylene-12,13-diphenyl-4,10-diazatricyclo[6.2.2.12,6]tridec-5-ene-3,9-dione 12k' was isolated following the **GP-2** using **11k** as reagent (47.9 mg, 0.20 mmol). Yield **26%** (12.6 mg, 0.026 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 7.12 (m, 6H), 7.08 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.00 – 6.77 (m, 2H), 6.22 (s, 1H), 5.17 (d, *J* = 2.2 Hz, 1H), 4.87 (d, *J* = 2.0 Hz, 1H), 4.40 (s, 1H), 3.93 (s, 1H), 3.40 (s, 1H), 2.89 (ddd, *J* = 9.6, 6.8, 4.5 Hz, 1H), 2.63 (d, *J* = 12.7 Hz, 1H), 2.53 – 2.46 (m, 1H), 2.43 (d, *J* = 12.7 Hz, 1H), 1.19 (s, 3H), 1.00 – 0.91 (m, 2H), 0.90 – 0.76 (m, 7H), 0.74 – 0.65 (m, 1H), 0.64 – 0.57 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 176.2 (Cq), 175.5 (Cq), 147.2 (Cq), 145.7 (Cq), 136.5 (Cq), 129.1 (2CH), 128.5 (brs, 4CH), 128.1 (2CH), 127.2 (CH), 127.2 (CH), 126.4 (CH), 120.5 (CH_2), 118.2 (Cq), 73.3 (CH), 56.8 (CH), 51.2 (Cq), 51.0 (CH_2), 49.1 (Cq), 46.9 (CH), 31.7 (CH), 28.9 (CH), 26.3 (CH_3), 21.8 (CH_3), 11.7 (CH_2), 6.6 (CH_2), 6.6 (CH_2), 5.0 (CH_2). **ESI-HRMS** calcd for $C_{32}H_{34}N_2NaO_2$ $[M+Na]^+$ 501.2512, found 501.2505.

5 References

(1) Nasini, R.; Brown, R.; Rée, A.; Miller, W. L.; Hewitt, J. T.; Dawson, H. M.; Knecht, E. Obituary Notices: John Young Buchanan, 1844–1925; Giacomo Luigi Ciamician, 1857–1922; Samuel Henry Davies, 1870–1925; William Henry Deering, 1848–1925; Francis Robert Japp, 1848–1925; Francis Jones, 1845–1925; Edmund Knecht, 1861–1925; William Robert Lang, 1870–1925; Frank George Pope, 1867–1925; Charles Etty Potter, 1880–1925; Robert Llewellyn Taylor, 1851–1925; Sir Edward Thorpe, 1845–1925. *J. Chem. Soc.* **1926**, *129* (0), 993–1050. https://doi.org/10.1039/JR9262900993.

(2) Büchi, G.; Inman, C. G.; Lipinsky, E. S. Light-Catalyzed Organic Reactions. I. The Reaction of Carbonyl Compounds with 2-Methyl-2-Butene in the Presence of Ultraviolet Light. *J Am Chem Soc* **1954**, *76* (17), 4327–4331. https://doi.org/10.1021/ja01646a024.

(3) HERRMANN, J. Heterogeneous Photocatalysis: In Situ Photoconductivity Study of TiO2 during Oxidation of Isobutane into Acetone. *Journal of Catalysis* **1979**, *60* (3), 369–377. https://doi.org/10.1016/0021-9517(79)90161-1.

(4) Kormann, Claudius.; Bahnemann, D. W.; Hoffmann, M. R. Photocatalytic Production of Hydrogen Peroxides and Organic Peroxides in Aqueous Suspensions of Titanium Dioxide, Zinc Oxide, and Desert Sand. *Environmental Science & Technology* **1988**, *22* (7), 798–806. https://doi.org/10.1021/es00172a009.

(5) HSIAO, C. Heterogeneous Photocatalysis: Degradation of Dilute Solutions of Dichloromethane (CH2Cl2), Chloroform (CHCl3), and Carbon Tetrachloride (CCl4) with Illuminated TiO2 Photocatalyst. *Journal of Catalysis* **1983**, *82* (2), 418–423. https://doi.org/10.1016/0021-9517(83)90208-7.

(6) Yuzawa, H.; Yoshida, T.; Yoshida, H. Gold Nanoparticles on Titanium Oxide Effective for Photocatalytic Hydrogen Formation under Visible Light. *Applied Catalysis B: Environmental* **2012**, *115–116*, 294–302. https://doi.org/10.1016/j.apcatb.2011.12.029.

(7) Xu, C.; Yang, W.; Guo, Q.; Dai, D.; Chen, M.; Yang, X. Molecular Hydrogen Formation from Photocatalysis of Methanol on TiO_2 (110). *J Am Chem Soc* **2013**, *135* (28), 10206–10209. https://doi.org/10.1021/ja4030963.

(8) Robert, D.; Malato, S. Solar Photocatalysis: A Clean Process for Water Detoxification. *Science of The Total Environment* **2002**, *291* (1–3), 85–97. https://doi.org/10.1016/S0048-9697(01)01094-4.

(9) Tucker, J. W.; Stephenson, C. R. J. Shining Light on Photoredox Catalysis: Theory and Synthetic Applications. *The Journal of Organic Chemistry* **2012**, *77* (4), 1617–1622. https://doi.org/10.1021/jo202538x.

(10) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *The Journal of Organic Chemistry* **2016**, *81* (16), 6898–6926. https://doi.org/10.1021/acs.joc.6b01449.

(11) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chemical Reviews* **2013**, *113* (7), 5322–5363. https://doi.org/10.1021/cr300503r.

(12) Nicewicz, D. A.; Nguyen, T. M. Recent Applications of Organic Dyes as Photoredox Catalysts in Organic Synthesis. *ACS Catalysis* **2014**, *4* (1), 355–360. https://doi.org/10.1021/cs400956a.

(13) Hockin, B. M.; Li, C.; Robertson, N.; Zysman-Colman, E. Photoredox Catalysts Based on Earth-Abundant Metal Complexes. *Catalysis Science & Technology* **2019**, *9* (4), 889–915. https://doi.org/10.1039/C8CY02336K.

(14) Larsen, C. B.; Wenger, O. S. Photoredox Catalysis with Metal Complexes Made from Earth-Abundant Elements. *Chemistry - A European Journal* **2018**, *24* (9), 2039–2058. https://doi.org/10.1002/chem.201703602.

(15) Balzani, V.; Bergamini, G.; Ceroni, P. Light: A Very Peculiar Reactant and Product. *Angewandte Chemie International Edition* **2015**, *54* (39), 11320–11337. https://doi.org/10.1002/anie.201502325.

(16) Mdluli, V.; Diluzio, S.; Lewis, J.; Kowalewski, J. F.; Connell, T. U.; Yaron, D.; Kowalewski, T.; Bernhard, S. High-Throughput Synthesis and Screening of Iridium(III) Photocatalysts for the Fast and Chemoselective Dehalogenation of Aryl Bromides. *ACS Catalysis* **2020**, *10* (13), 6977–6987. https://doi.org/10.1021/acscatal.0c02247.

(17) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. Visible-Light Photoredox Catalysis: Aza-Henry Reactions via C−H Functionalization. *J Am Chem Soc* **2010**, *132* (5), 1464–1465. https://doi.org/10.1021/ja909145y.

(18) Ischay, M. A.; Lu, Z.; Yoon, T. P. [2+2] Cycloadditions by Oxidative Visible Light Photocatalysis. *J Am Chem Soc* **2010**, *132* (25), 8572–8574. https://doi.org/10.1021/ja103934y.

(19) Roth, H.; Romero, N.; Nicewicz, D. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. *Synlett* **2015**, *27* (05), 714–723. https://doi.org/10.1055/s-0035-1561297.

(20) Turro, N. J. Energy Transfer Processes. *Pure and Applied Chemistry* **1977**, *49* (4), 405–429. https://doi.org/10.1351/pac197749040405.

(21) Verhoeven, J. W. Glossary of Terms Used in Photochemistry (IUPAC Recommendations 1996). *Pure and Applied Chemistry* **1996**, *68* (12), 2223–2286. https://doi.org/10.1351/pac199668122223.

(22) Şener, M.; Strümpfer, J.; Hsin, J.; Chandler, D.; Scheuring, S.; Hunter, C. N.; Schulten, K. Förster Energy Transfer Theory as Reflected in the Structures of Photosynthetic Light-Harvesting Systems. *ChemPhysChem* **2011**, *12* (3), 518–531. https://doi.org/10.1002/cphc.201000944.

(23) Dexter, D. L. A Theory of Sensitized Luminescence in Solids. *The Journal of Chemical Physics* **1953**, *21* (5), 836–850. https://doi.org/10.1063/1.1699044.

(24) Strieth-Kalthoff, F.; Glorius, F. Triplet Energy Transfer Photocatalysis: Unlocking the Next Level. *Chem* **2020**, *6* (8), 1888–1903. https://doi.org/10.1016/j.chempr.2020.07.010.

(25) Hammond, G. S.; Saltiel, Jack.; Lamola, A. A.; Turro, N. J.; Bradshaw, J. S.; Cowan, D. O.; Counsell, R. C.; Vogt, Volker.; Dalton, Christopher. Mechanisms of Photochemical

Reactions in Solution. XXII. [1] Photochemical *Cis-Trans* Isomerization. *J Am Chem Soc* **1964**, *86* (16), 3197–3217. https://doi.org/10.1021/ja01070a002.

(26) Neveselý, T.; Wienhold, M.; Molloy, J. J.; Gilmour, R. Advances in the *E* → *Z* Isomerization of Alkenes Using Small Molecule Photocatalysts. *Chemical Reviews* **2021**, acs.chemrev.1c00324. https://doi.org/10.1021/acs.chemrev.1c00324.

(27) Ha, S.; Lee, Y.; Kwak, Y.; Mishra, A.; Yu, E.; Ryou, B.; Park, C.-M. Alkyne–Alkene [2 + 2] Cycloaddition Based on Visible Light Photocatalysis. *Nature Communications* **2020**, *11* (1), 2509. https://doi.org/10.1038/s41467-020-16283-9.

(28) Lu, Z.; Yoon, T. P. Visible Light Photocatalysis of [2+2] Styrene Cycloadditions by Energy Transfer. *Angewandte Chemie International Edition* **2012**, *51* (41), 10329–10332. https://doi.org/10.1002/anie.201204835.

(29) Alonso, R.; Bach, T. A Chiral Thioxanthone as an Organocatalyst for Enantioselective [2+2] Photocycloaddition Reactions Induced by Visible Light. *Angewandte Chemie International Edition* **2014**, *53* (17), 4368–4371. https://doi.org/10.1002/anie.201310997.

(30) Blum, T. R.; Miller, Z. D.; Bates, D. M.; Guzei, I. A.; Yoon, T. P. Enantioselective Photochemistry through Lewis Acid–Catalyzed Triplet Energy Transfer. *Science (1979)* **2016**, *354* (6318), 1391–1395. https://doi.org/10.1126/science.aai8228.

(31) Münster, N.; Parker, N. A.; van Dijk, L.; Paton, R. S.; Smith, M. D. Visible Light Photocatalysis of 6π Heterocyclization. *Angewandte Chemie International Edition* **2017**, *56* (32), 9468–9472. https://doi.org/10.1002/anie.201705333.

(32) Ghosh, I.; Shaikh, R. S.; König, B. Sensitization-Initiated Electron Transfer for Photoredox Catalysis. *Angewandte Chemie International Edition* **2017**, *56* (29), 8544–8549. https://doi.org/10.1002/anie.201703004.

(33) Marchini, M.; Bergamini, G.; Cozzi, P. G.; Ceroni, P.; Balzani, V. Photoredox Catalysis: The Need to Elucidate the Photochemical Mechanism. *Angewandte Chemie International Edition* **2017**, *56* (42), 12820–12821. https://doi.org/10.1002/anie.201706217.

(34) Ghosh, I.; Bardagi, J. I.; König, B. Reply to "Photoredox Catalysis: The Need to Elucidate the Photochemical Mechanism." *Angewandte Chemie International Edition* **2017**, *56* (42), 12822–12824. https://doi.org/10.1002/anie.201707594.

(35) Ohkubo, K.; Fujimoto, A.; Fukuzumi, S. Visible-Light-Induced Oxygenation of Benzene by the Triplet Excited State of 2,3-Dichloro-5,6-Dicyano- *p* -Benzoquinone. *J Am Chem Soc* **2013**, *135* (14), 5368–5371. https://doi.org/10.1021/ja402303k.

(36) Grampp, G. The Marcus Inverted Region from Theory to Experiment. *Angewandte Chemie International Edition in English* **1993**, *32* (5), 691–693. https://doi.org/10.1002/anie.199306911.

(37) Marcus, R. A. Electron Transfer Reactions in Chemistry: Theory and Experiment (Nobel Lecture). *Angewandte Chemie International Edition in English* **1993**, *32* (8), 1111–1121. https://doi.org/10.1002/anie.199311113.

(38) Jung, M. E.; Piizzi, G. *Gem* -Disubstituent Effect: Theoretical Basis and Synthetic Applications. *Chemical Reviews* **2005**, *105* (5), 1735–1766. https://doi.org/10.1021/cr940337h.

(39) Mutra, M. R.; Kudale, V. S.; Li, J.; Tsai, W.-H.; Wang, J.-J. Alkene *versus* Alkyne Reactivity in Unactivated 1,6-Enynes: Regio- and Chemoselective Radical Cyclization with Chalcogens under Metal- and Oxidant-Free Conditions. *Green Chemistry* **2020**, *22* (7), 2288–2300. https://doi.org/10.1039/D0GC00321B.

(40) Hou, H.; Sun, Y.; Pan, Y.; Yu, H.; Han, Y.; Shi, Y.; Yan, C.; Zhu, S. Visible-Light Mediated Diarylselenylative Cyclization of 1,6-Enynes. *The Journal of Organic Chemistry* **2021**, *86* (1), 1273–1280. https://doi.org/10.1021/acs.joc.0c02529.

(41) Lanzi, M.; Cañeque, T.; Marchiò, L.; Maggi, R.; Bigi, F.; Malacria, M.; Maestri, G. Alternative Routes to Tricyclic Cyclohexenes with Trinuclear Palladium Complexes. *ACS Catalysis* **2018**, *8* (1). https://doi.org/10.1021/acscatal.7b03366.

(42) Zhang, T.; Fu, L.; Gutekunst, W. R. Practical Synthesis of Functional Metathesis Initiators Using Enynes. *Macromolecules* **2018**, *51* (16). https://doi.org/10.1021/acs.macromol.8b00866.

(43) Ren, S. C.; Zhang, F. L.; Qi, J.; Huang, Y. S.; Xu, A. Q.; Yan, H. Y.; Wang, Y. F. Radical Borylation/Cyclization Cascade of 1,6-Enynes for the Synthesis of Boron-Handled Hetero- and Carbocycles. *J Am Chem Soc* **2017**, *139* (17). https://doi.org/10.1021/jacs.7b01889.

(44) Cecchini, C.; Lanzi, M.; Cera, G.; Malacria, M.; Maestri, G. Complementary Reactivity of 1,6-Enynes with All-Metal Aromatic Trinuclear Complexes and Carboxylic Acids. *Synthesis (Germany)* **2019**, *51* (5). https://doi.org/10.1055/s-0037-1611653.

(45) Orlandi, M.; Hilton, M. J.; Yamamoto, E.; Toste, F. D.; Sigman, M. S. Mechanistic Investigations of the Pd(0)-Catalyzed Enantioselective 1,1-Diarylation of Benzyl Acrylates. *J Am Chem Soc* **2017**, *139* (36), 12688–12695. https://doi.org/10.1021/jacs.7b06917.

(46) Namyslo, J. C.; Kaufmann, D. E. The Application of Cyclobutane Derivatives in Organic Synthesis. *Chemical Reviews* **2003**, *103* (4), 1485–1538. https://doi.org/10.1021/cr010010y.

(47) Li, J.; Gao, K.; Bian, M.; Ding, H. Recent Advances in the Total Synthesis of Cyclobutane-Containing Natural Products. *Organic Chemistry Frontiers* **2020**, *7* (1), 136–154. https://doi.org/10.1039/C9QO01178A.

(48) Willstätter, R.; Bruce, J. Zur Kenntnis Der Cyclobutanreihe. *Berichte der deutschen chemischen Gesellschaft* **1907**, *40* (4), 3979–3999. https://doi.org/10.1002/cber.19070400407.

(49) SMITH, W. B. Some Dehalogenation Reactions of 1,4-Dibromobutane [1]. *The Journal of Organic Chemistry* **1958**, *23* (4), 509–512. https://doi.org/10.1021/jo01098a001.

(50) 1,1-CYCLOBUTANEDICARBOXYLIC ACID AND CYCLOBUTANECARBOXYLIC ACID. *Organic Syntheses* **1943**, *23*, 16. https://doi.org/10.15227/orgsyn.023.0016.

(51) Mercer, J. A. M.; Cohen, C. M.; Shuken, S. R.; Wagner, A. M.; Smith, M. W.; Moss, F. R.; Smith, M. D.; Vahala, R.; Gonzalez-Martinez, A.; Boxer, S. G.; Burns, N. Z. Chemical

Synthesis and Self-Assembly of a Ladderane Phospholipid. *J Am Chem Soc* **2016**, *138* (49), 15845–15848. https://doi.org/10.1021/jacs.6b10706.

(52) Salomon, R. G.; Kochi, J. K. Copper(I) Catalysis in Photocycloadditions. I. Norbornene. *J Am Chem Soc* **1974**, *96* (4), 1137–1144. https://doi.org/10.1021/ja00811a030.

(53) Ruider, S. A.; Sandmeier, T.; Carreira, E. M. Total Synthesis of (±)-Hippolachnin A. *Angewandte Chemie International Edition* **2015**, *54* (8), 2378–2382. https://doi.org/10.1002/anie.201410419.

(54) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. Asymmetric [2 + 2] Cycloaddition Reaction Catalyzed by a Chiral Titanium Reagent. *J Am Chem Soc* **1992**, *114* (23), 8869–8885. https://doi.org/10.1021/ja00049a020.

(55) Ito, H.; Hasegawa, M.; Takenaka, Y.; Kobayashi, T.; Iguchi, K. Enantioselective Total Synthesis of (+)-Tricycloclavulone. *J Am Chem Soc* **2004**, *126* (14), 4520–4521. https://doi.org/10.1021/ja049750p.

(56) Kang, T.; Ge, S.; Lin, L.; Lu, Y.; Liu, X.; Feng, X. A Chiral *N* , *N′* -Dioxide–Zn ^{II} Complex Catalyzes the Enantioselective [2+2] Cycloaddition of Alkynones with Cyclic Enol Silyl Ethers. *Angewandte Chemie* **2016**, *128* (18), 5631–5634. https://doi.org/10.1002/ange.201600801.

(57) Iwata, S.; Hamura, T.; Suzuki, K. Siloxy(Trialkoxy)Ethene Undergoes Regioselective [2+2] Cycloaddition to Ynones and Ynoates En Route to Functionalized Cyclobutenediones. *Chemical Communications* **2010**, *46* (29), 5316. https://doi.org/10.1039/c0cc00883d.

(58) Ishihara, K.; Fushimi, M. Catalytic Enantioselective [2 + 4] and [2 + 2] Cycloaddition Reactions with Propiolamides. *J Am Chem Soc* **2008**, *130* (24), 7532–7533. https://doi.org/10.1021/ja8015318.

(59) Hu, J.-L.; Feng, L.-W.; Wang, L.; Xie, Z.; Tang, Y.; Li, X. Enantioselective Construction of Cyclobutanes: A New and Concise Approach to the Total Synthesis of (+)-Piperarborenine B. *J Am Chem Soc* **2016**, *138* (40), 13151–13154. https://doi.org/10.1021/jacs.6b08279.

(60) Rasik, C. M.; Brown, M. K. Lewis Acid-Promoted Ketene–Alkene [2 + 2] Cycloadditions. *J Am Chem Soc* **2013**, *135* (5), 1673–1676. https://doi.org/10.1021/ja3103007.

(61) Liu, L.; Ward, R. M.; Schomaker, J. M. Mechanistic Aspects and Synthetic Applications of Radical Additions to Allenes. *Chemical Reviews* **2019**, *119* (24), 12422–12490. https://doi.org/10.1021/acs.chemrev.9b00312.

(62) Blieck, R.; Taillefer, M.; Monnier, F. Metal-Catalyzed Intermolecular Hydrofunctionalization of Allenes: Easy Access to Allylic Structures via the Selective Formation of C–N, C–C, and C–O Bonds. *Chemical Reviews* **2020**, *120* (24), 13545–13598. https://doi.org/10.1021/acs.chemrev.0c00803.

(63) Alonso, J. M.; Almendros, P. Deciphering the Chameleonic Chemistry of Allenols: Breaking the Taboo of a Onetime Esoteric Functionality. *Chemical Reviews* **2021**, *121* (7), 4193–4252. https://doi.org/10.1021/acs.chemrev.0c00986.

(64) Miao, R.; Gramani, S. G.; Lear, M. J. Stereocontrolled Entry to the Tricyclo[3.3.0]Oxoheptane Core of Bielschowskysin by a [2+2] Cycloaddition of an

Allene-Butenolide. *Tetrahedron Letters* **2009**, *50* (15), 1731–1733. https://doi.org/10.1016/j.tetlet.2009.01.131.

(65) Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fujii, N.; Tanaka, T. A Highly Regio- and Stereoselective Formation of Bicyclo[4.2.0]Oct-5-Ene Derivatives through Thermal Intramolecular [2 + 2] Cycloaddition of Allenes. *The Journal of Organic Chemistry* **2007**, *72* (12), 4378–4389. https://doi.org/10.1021/jo0700528.

(66) Luzung, M. R.; Mauleón, P.; Toste, F. D. Gold(I)-Catalyzed [2 + 2]-Cycloaddition of Allenenes. *J Am Chem Soc* **2007**, *129* (41), 12402–12403. https://doi.org/10.1021/ja075412n.

(67) Busacca, C. A.; Dong, Y. A Facile Synthesis of 4-Aryl-2,3-Dihydropyrroles. *Tetrahedron Letters* **1996**, *37* (23), 3947–3950. https://doi.org/10.1016/0040-4039(96)00749-6.

(68) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. Efficient Homologation of Acetylenes to Allenes. *J. Chem. Soc., Chem. Commun.* **1979**, No. 19, 859–860. https://doi.org/10.1039/C39790000859.

(69) Luo, H.; Ma, S. CuI-Catalyzed Synthesis of Functionalized Terminal Allenes from 1-Alkynes. *European Journal of Organic Chemistry* **2013**, *2013* (15), 3041–3048. https://doi.org/10.1002/ejoc.201201696.

(70) Kuang, J.; Ma, S. One-Pot Synthesis of 1,3-Disubstituted Allenes from 1-Alkynes, Aldehydes, and Morpholine. *J Am Chem Soc* **2010**, *132* (6), 1786–1787. https://doi.org/10.1021/ja910503k.

(71) Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fujii, N.; Tanaka, T. A Highly Regio- and Stereoselective Formation of Bicyclo[4.2.0]Oct-5-Ene Derivatives through Thermal Intramolecular [2 + 2] Cycloaddition of Allenes. *The Journal of Organic Chemistry* **2007**, *72* (12), 4378–4389. https://doi.org/10.1021/jo0700528.

(72) Tang, X.; Zhu, C.; Cao, T.; Kuang, J.; Lin, W.; Ni, S.; Zhang, J.; Ma, S. Cadmium Iodide-Mediated Allenylation of Terminal Alkynes with Ketones. *Nature Communications* **2013**, *4* (1), 2450. https://doi.org/10.1038/ncomms3450.

(73) Kuang, J.; Tang, X.; Ma, S. Zinc Diiodide-Promoted Synthesis of Trisubstituted Allenes from Propargylic Amines. *Organic Chemistry Frontiers* **2015**, *2* (5), 470–475. https://doi.org/10.1039/C5QO00047E.

(74) Hurtley, A. E.; Lu, Z.; Yoon, T. P. [2+2] Cycloaddition of 1,3-Dienes by Visible Light Photocatalysis. *Angewandte Chemie International Edition* **2014**, *53* (34), 8991–8994. https://doi.org/10.1002/anie.201405359.

(75) Hu, N.; Jung, H.; Zheng, Y.; Lee, J.; Zhang, L.; Ullah, Z.; Xie, X.; Harms, K.; Baik, M.; Meggers, E. Catalytic Asymmetric Dearomatization by Visible-Light-Activated [2+2] Photocycloaddition. *Angewandte Chemie International Edition* **2018**, *57* (21), 6242–6246. https://doi.org/10.1002/anie.201802891.

(76) Münster, N.; Parker, N. A.; van Dijk, L.; Paton, R. S.; Smith, M. D. Visible Light Photocatalysis of 6π Heterocyclization. *Angewandte Chemie International Edition* **2017**, *56* (32), 9468–9472. https://doi.org/10.1002/anie.201705333.

(77) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. Visible-Light Excitation of Iminium Ions Enables the Enantioselective Catalytic β-Alkylation of Enals. *Nature Chemistry* **2017**, *9* (9), 868–873. https://doi.org/10.1038/nchem.2748.

(78) Hammer, N.; Christensen, M. L.; Chen, Y.; Naharro, D.; Liu, F.; Jørgensen, K. A.; Houk, K. N. An Experimental Stereoselective Photochemical [1s,3s]-Sigmatropic Silyl Shift and the Existence of Silyl/Allyl Conical Intersections. *J Am Chem Soc* **2020**, *142* (13), 6030–6035. https://doi.org/10.1021/jacs.9b11579.

(79) Bernardi, F.; Olivucci, M.; Robb, M. A.; Tonachini, G. Can a Photochemical Reaction Be Concerted? A Theoretical Study of the Photochemical Sigmatropic Rearrangement of but-1-Ene. *J Am Chem Soc* **1992**, *114* (14), 5805–5812. https://doi.org/10.1021/ja00040a049.

(80) Wilsey, S.; Houk, K. N. H/Allyl and Alkyl/Allyl Conical Intersections: Ubiquitous Control Elements in Photochemical Sigmatropic Shifts. *J Am Chem Soc* **2000**, *122* (11), 2651–2652. https://doi.org/10.1021/ja993302d.

(81) Huang, X.; Ma, S. Allenation of Terminal Alkynes with Aldehydes and Ketones. *Accounts of Chemical Research* **2019**, *52* (5), 1301–1312. https://doi.org/10.1021/acs.accounts.9b00023.

(82) Stacey, F. W.; Sauer, J. C.; McKusick, B. C. The Radiation-Induced Isomerization of N-Alkyl-N-Vinylsulfonamides [1]. *J Am Chem Soc* **1959**, *81* (4), 987–992. https://doi.org/10.1021/ja01513a058.

(83) Lanzi, M.; Santacroce, V.; Balestri, D.; Marchiò, L.; Bigi, F.; Maggi, R.; Malacria, M.; Maestri, G. Visible-Light-Promoted Polycyclizations of Dienynes. *Angewandte Chemie - International Edition* **2019**, *58* (20). https://doi.org/10.1002/anie.201902837.

(84) Voutyritsa, E.; Kokotos, C. G. Green Metal-Free Photochemical Hydroacylation of Unactivated Olefins. *Angewandte Chemie International Edition* **2020**, *59* (4), 1735–1741. https://doi.org/10.1002/anie.201912214.

(85) Lübbesmeyer, M.; Mackay, E. G.; Raycroft, M. A. R.; Elfert, J.; Pratt, D. A.; Studer, A. Base-Promoted C–C Bond Activation Enables Radical Allylation with Homoallylic Alcohols. *J Am Chem Soc* **2020**, *142* (5), 2609–2616. https://doi.org/10.1021/jacs.9b12343.

(86) Zhang, H.; Hay, E. ben; Geib, S. J.; Curran, D. P. Radical Cyclizations of Cyclic Ene Sulfonamides Occur with β-Elimination of Sulfonyl Radicals to Form Polycyclic Imines. *J Am Chem Soc* **2013**, *135* (44), 16610–16617. https://doi.org/10.1021/ja408387d.

(87) Darmency, V.; Renaud, P. Alkylation of Ethyl Pyruvate <I>Via</I> Reductive Coupling of Alkenes and Ethyl 2-(Benzenesulfonylamino)Acrylate. *CHIMIA International Journal for Chemistry* **2005**, *59* (3), 109–110. https://doi.org/10.2533/000942905777676722.

(88) Cossy, J.; Cases, M.; Gomez Pardo, D. Approaches to a Synthesis of α-Kainic Acid. *Tetrahedron* **1999**, *55* (19), 6153–6166. https://doi.org/10.1016/S0040-4020(99)00284-7.

(89) Walsh, C. T.; Moore, B. S. Enzymatic Cascade Reactions in Biosynthesis. *Angewandte Chemie International Edition* **2019**, *58* (21), 6846–6879. https://doi.org/10.1002/anie.201807844.

(90) Robinson, R. LXIII.—A Synthesis of Tropinone. *J. Chem. Soc., Trans.* **1917**, *111* (0), 762–768. https://doi.org/10.1039/CT9171100762.

(91) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angewandte Chemie International Edition* **2006**, *45* (43), 7134–7186. https://doi.org/10.1002/anie.200601872.

(92) Biemolt, J.; Ruijter, E. Advances in Palladium-Catalyzed Cascade Cyclizations. *Advanced Synthesis & Catalysis* **2018**, *360* (20), 3821–3871. https://doi.org/10.1002/adsc.201800526.

(93) Zakarian, A.; Batch, A.; Holton, R. A. A Convergent Total Synthesis of Hemibrevetoxin B. *J Am Chem Soc* **2003**, *125* (26), 7822–7824. https://doi.org/10.1021/ja029225v.

(94) Pfeiffer, M. W. B.; Phillips, A. J. Total Synthesis of (+)-Cyanthiwigin U. *J Am Chem Soc* **2005**, *127* (15), 5334–5335. https://doi.org/10.1021/ja0509836.

(95) Curran, D. P.; Chen, M.-H. Radical-Initiated Polyolefinic Cyclizations in Condensed Cyclopentanoid Synthesis. Total Synthesis of (±)-Δ9(12)-Capnellene. *Tetrahedron Letters* **1985**, *26* (41), 4991–4994. https://doi.org/10.1016/S0040-4039(01)80834-0.

(96) Huang, H.-M.; McDouall, J. J. W.; Procter, D. J. SmI2-Catalysed Cyclization Cascades by Radical Relay. *Nature Catalysis* **2019**, *2* (3), 211–218. https://doi.org/10.1038/s41929-018-0219-x.

(97) Zhang, Y.; Sun, K.; Lv, Q.; Chen, X.; Qu, L.; Yu, B. Recent Applications of Radical Cascade Reaction in the Synthesis of Functionalized 1-Indenones. *Chinese Chemical Letters* **2019**, *30* (7), 1361–1368. https://doi.org/10.1016/j.cclet.2019.03.034.

(98) Huang, H.-M.; Garduño-Castro, M. H.; Morrill, C.; Procter, D. J. Catalytic Cascade Reactions by Radical Relay. *Chemical Society Reviews* **2019**, *48* (17), 4626–4638. https://doi.org/10.1039/C8CS00947C.

(99) Plesniak, M. P.; Huang, H.-M.; Procter, D. J. Radical Cascade Reactions Triggered by Single Electron Transfer. *Nature Reviews Chemistry* **2017**, *1* (10), 0077. https://doi.org/10.1038/s41570-017-0077.

(100) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chemical Reviews* **2016**, *116* (17), 10075–10166. https://doi.org/10.1021/acs.chemrev.6b00057.

(101) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. Energy Transfer Catalysis Mediated by Visible Light: Principles, Applications, Directions. *Chemical Society Reviews* **2018**, *47* (19), 7190–7202. https://doi.org/10.1039/C8CS00054A.

(102) Augustine, J. K.; Bombrun, A.; Venkatachaliah, S.; Jothi, A. Titanium Mediated Olefination of Aldehydes with α-Haloacetates: An Exceptionally Stereoselective and General Approach to (Z)-α-Haloacrylates. *Organic & Biomolecular Chemistry* **2013**, *11* (46), 8065. https://doi.org/10.1039/c3ob41592a.

(103) Navarro-Vázquez, A. Why Base-Catalyzed Isomerization of *N* -Propargyl Amides Yields Mostly Allenamides Rather than Ynamides. *Beilstein Journal of Organic Chemistry* **2015**, *11*, 1441–1446. https://doi.org/10.3762/bjoc.11.156.

(104) Pallini, F.; Sangalli, E.; Sassi, M.; Roth, P. M. C.; Mattiello, S.; Beverina, L. Selective Photoredox Direct Arylations of Aryl Bromides in Water in a Microfluidic Reactor.

Organic & Biomolecular Chemistry **2021**, *19* (13), 3016–3023. https://doi.org/10.1039/D1OB00050K.

(105) Liu, Y.-Q.; Tian, J.; Qian, K.; Zhao, X.-B.; Morris-Natschke, S. L.; Yang, L.; Nan, X.; Tian, X.; Lee, K.-H. Recent Progress on C-4-Modified Podophyllotoxin Analogs as Potent Antitumor Agents. *Medicinal Research Reviews* **2015**, *35* (1), 1–62. https://doi.org/10.1002/med.21319.

(106) Fan, H.; Zhu, Z.; Xian, H.; Wang, H.; Chen, B.; Tang, Y.-J.; Tang, Y.; Liang, X. Insight Into the Molecular Mechanism of Podophyllotoxin Derivatives as Anticancer Drugs. *Frontiers in Cell and Developmental Biology* **2021**, *9*. https://doi.org/10.3389/fcell.2021.709075.

(107) Connell, T. U.; Fraser, C. L.; Czyz, M. L.; Smith, Z. M.; Hayne, D. J.; Doeven, E. H.; Agugiaro, J.; Wilson, D. J. D.; Adcock, J. L.; Scully, A. D.; Gómez, D. E.; Barnett, N. W.; Polyzos, A.; Francis, P. S. The Tandem Photoredox Catalysis Mechanism of $[Ir(Ppy)_2(Dtb\text{-}Bpy)]^+$ Enabling Access to Energy Demanding Organic Substrates. *J Am Chem Soc* **2019**, *141* (44), 17646–17658. https://doi.org/10.1021/jacs.9b07370.

(108) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. Total Synthesis of Taxol. *Nature* **1994**, *367* (6464), 630–634. https://doi.org/10.1038/367630a0.

(109) Vaishampayan, U.; Parchment, R. E.; Jasti, B. R.; Hussain, M. Taxanes: An Overview of the Pharmacokinetics and Pharmacodynamics. *Urology* **1999**, *54* (6), 22–29. https://doi.org/10.1016/S0090-4295(99)00451-3.

(110) Hwang, M.; Seiwert, T. Y. Are Taxanes the Future for Head and Neck Cancer? Pragmatism in the Immunotherapy Era. *The Lancet Oncology* **2021**, *22* (4), 413–415. https://doi.org/10.1016/S1470-2045(21)00121-2.

(111) Parsaee, F.; Senarathna, M. C.; Kannangara, P. B.; Alexander, S. N.; Arche, P. D. E.; Welin, E. R. Radical Philicity and Its Role in Selective Organic Transformations. *Nature Reviews Chemistry* **2021**, *5* (7), 486–499. https://doi.org/10.1038/s41570-021-00284-3.

(112) Shu, W.; Nevado, C. Visible-Light-Mediated Remote Aliphatic C−H Functionalizations through a 1,5-Hydrogen Transfer Cascade. *Angewandte Chemie International Edition* **2017**, *56* (7), 1881–1884. https://doi.org/10.1002/anie.201609885.

(113) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic Alkylation of Remote C–H Bonds Enabled by Proton-Coupled Electron Transfer. *Nature* **2016**, *539* (7628), 268–271. https://doi.org/10.1038/nature19811.

(114) Guo, W.; Wang, Q.; Zhu, J. Visible Light Photoredox-Catalysed Remote C–H Functionalisation Enabled by 1,5-Hydrogen Atom Transfer (1,5-HAT). *Chemical Society Reviews* **2021**, *50* (13), 7359–7377. https://doi.org/10.1039/D0CS00774A.

(115) Augustine, J. K.; Bombrun, A.; Venkatachaliah, S.; Jothi, A. Titanium Mediated Olefination of Aldehydes with α-Haloacetates: An Exceptionally Stereoselective and General Approach to (Z)-α-Haloacrylates. *Organic & Biomolecular Chemistry* **2013**, *11* (46). https://doi.org/10.1039/c3ob41592a.

(116) Hioe, J.; Zipse, H. Radical Stability and Its Role in Synthesis and Catalysis. *Organic & Biomolecular Chemistry* **2010**, *8* (16), 3609. https://doi.org/10.1039/c004166a.