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Gold-catalyzed cycloisomerizations of ene-ynamides

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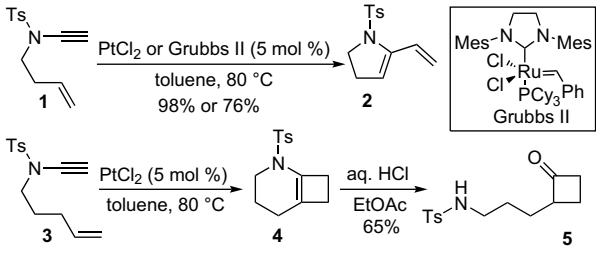
ABSTRACT

The gold-catalyzed cycloisomerizations of 1,6-ene-ynamides proceed under mild conditions and lead to cyclobutanones from terminal or trimethylsilyl substituted ynamides, or to carbonyl compounds bearing a 2,3-methanopyrrolidine subunit from substrates possessing a propargylic alcohol moiety. High diastereoselectivities are observed with 1,6-ene-ynamides having a stereocenter at the α or β position of the nitrogen atom.

1. Introduction

In the presence of transition metal catalysts, 1,*n*-enynes can undergo an impressive number of chemical transformations leading to highly functionalized cyclic or polycyclic complex molecules that could not be so easily and efficiently attained by other routes.[1–3] Due to their exceptional ability to selectively coordinate to alkynes and activate the triple bond toward intramolecular nucleophilic attack by alkenes, gold salts and complexes have been shown to be highly active catalysts for enyne cycloisomerizations.[2–5] In recent years, remarkable achievements in this field have been reported,[2–5] but the gold-catalyzed cycloisomerizations of the triisopropylsilyl ethers derived from ene-ynols were the only examples of such reactions involving enynes with a heterosubstituted carbon–carbon triple bond.[4n] During the last decade, ynamides, which possess an electron-withdrawing group on the nitrogen atom and constitute a stable class of acetylenic amines derivatives, have been successfully used as partners in synthetically useful metal-catalyzed processes.[6] Among them, Ru, Rh, Pd, Cu, and Pt have been employed,[6] however, before 2006, there was no report concerning the reactivity of ynamides in the presence of gold catalysts[7] and we were thus interested in investigating the gold-catalyzed cycloisomerizations of ene-ynamides.

Previously, the cycloisomerization of ene-ynamides had been investigated with $PtCl_2$ as a catalyst.[8] It was reported that treatment of the 1,6-ene-ynamide **1** with a catalytic amount of $PtCl_2$ [(5 mol %), toluene, 80 °C] led to the five-membered ring nitrogen heterocycle **2** (98%), possessing a dienamide moiety.[8] This compound had also been synthesized by ring-closing metathesis of ene-ynamide **1** catalyzed by Grubbs' second generation catalyst.[9] However, under the same conditions, the 1,7-ene-ynamide **3** exhibited a different behavior as the cyclobutenamide **4**, having a tetrasubstituted alkene, was formed. This rather unstable compound could be isolated in modest yield (44%) but a hydrolytic work-up under acidic conditions led to cyclobutanone **5** in a better yield (65%) (Scheme 1).[8]



Scheme 1.

In the original mechanistic proposal, the authors suggested that a platinum cyclopropylcarbene intermediate of type **A** (M=$PtCl_2$), generated by electrophilic activation of the ynamide and concomitant nucleophilic attack of the alkene, would undergo ring-expansion to form a cyclobutyl cation **B**.[8] The latter species should benefit from stabilization by the nitrogen atom compared to the non-heterosubstituted series. After demetalation and regeneration of the catalyst, a cyclobutenamide of type **C** would be formed and its evolution would depend on the ring size. In the case of the 1,6-ene-ynamide **1**, the strained cyclobutenamide **C** (n=1) would preferentially undergo electrocyclic ring-opening to generate dienamide **2**. However, by analogy with mechanistic investigations carried out in the non-heterosubstituted series, dienamide **2** could also result from the skeletal rearrangement of the platinum cyclopropylcarbene **A** (M=$PtCl_2$), through intermediates **D** and/or

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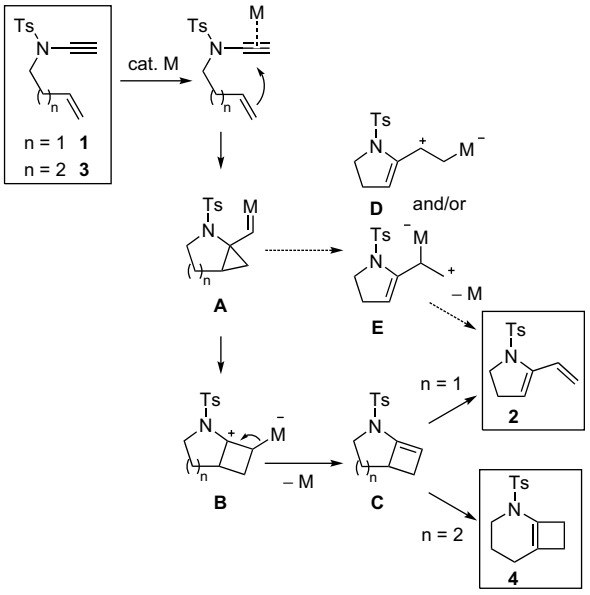
E.[1–3,4a–g] For the 1,7-ene-ynamide **3**, the less strained cyclobutenamide intermediate **C** (n=2) could undergo alkene migration to generate cyclobutenamide **4** bearing a tetrasubstituted double bond (Scheme 2).[8]



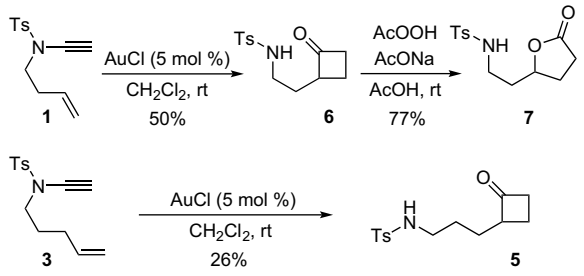
Scheme 2.

Assuming the intermediacy of cyclobutenamides of type **C** in the cycloisomerization of ene-ynamides **1** and **3**, we hypothesized that the use of milder conditions may prevent their electrocyclic ring-opening or their isomerization. Although platinum and gold catalysts are known to trigger similar processes, gold-catalyzed reactions generally proceed under milder conditions.[2–5] Thus, we decided to explore the reactivity of ene-ynamides in the presence of gold catalysts to see whether there would be a difference compared to the platinum-catalyzed reactions. Herein, we report a full account of our investigations on gold-catalyzed cycloisomerizations of 1,6-ene-ynamides and their application to the diastereoselective synthesis of cyclobutanones, γ-lactones as well as functionalized 2,3-methanopyrrolidines.[10]

2. Gold-catalyzed cycloisomerizations of 1,6-ene-ynamides

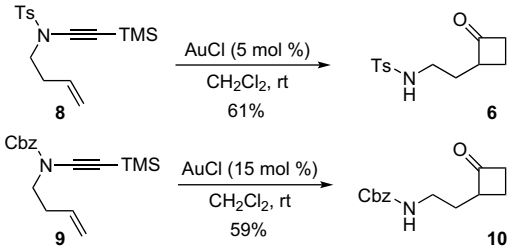
2.1. Preliminary investigations

In our initial experiments, the 1,6-ene-ynamide **1**[8,9] was treated with a catalytic amount of AuCl [(5–10 mol %), CH_2Cl_2, rt, 12–24 h]. Under these conditions, we found that dienamide **2** was formed as a minor product (<5–10%) whereas cyclobutanone **6** was isolated as the major compound in 50% yield. The use of $AuCl_3$ [(5 mol %), MeCN, rt] led to the same result and in fact an Au(III) species may always be the actual catalyst as AuCl is known to disproportionate to Au(III) and Au(0) in CH_2Cl_2.[11] However, the use of AuCl was preferred as it is less hygroscopic than $AuCl_3$ and hence easier to handle and weigh on a small scale. The formation of cyclobutanone **6** was also confirmed by its conversion to γ-lactone **7** (77%) through a Baeyer–Villiger oxidation (AcOOH, AcONa, AcOH, rt).[12] Thus, the gold-catalyzed reaction of the 1,6-ene-ynamide **1** effectively proceeded under mild conditions and provided a product different from the one generated by the platinum-catalyzed process.[8] In a similar fashion, the 1,7-ene-ynamide **3** was also treated with AuCl [(5 mol %), CH_2Cl_2, rt] but a slow reaction was observed and cyclobutanone **5** was isolated in low yield (26%), which was not improved by heating at reflux. As compound **5** was obtained in a much better yield by the platinum-catalyzed reaction,[8] our subsequent investigations exclusively focused on the gold-catalyzed cycloisomerizations of 1,6-ene-ynamides (Scheme 3).



Scheme 3.

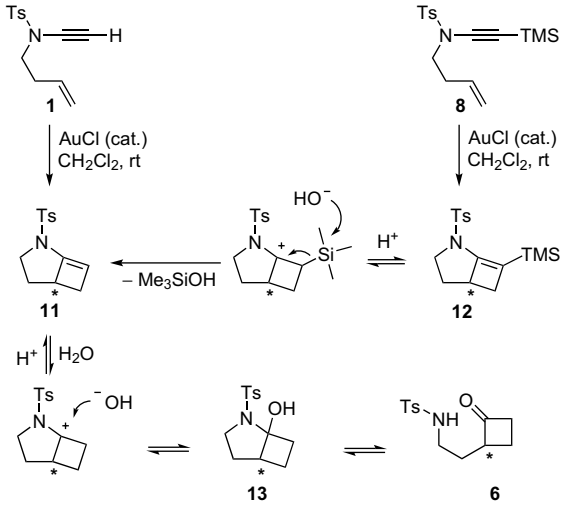
Interestingly, upon treatment with a catalytic amount of AuCl (5–15 mol %), the silylated ene-ynamides **8** and **9**, bearing a tosyl group or a benzyloxycarbonyl group on the nitrogen atom, were also cleanly converted to the cyclobutanones **6** (61%) and **10** (59%), respectively. The opportunity to carry out those transformations directly with trimethylsilyl-ynamides is particularly attractive since these compounds are generally more stable than terminal ynamides and, further more, no additional desilylation step was required (Scheme 4).



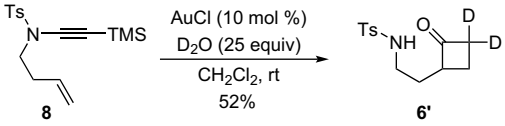
Scheme 4.

The gold-catalyzed cycloisomerizations of the 1,6-ene-ynamides **1** or **8** presumably involve gold cyclopropylcarbene intermediates of type **A** (Scheme 2, M=AuCl) that evolve by ring-expansion and provide cyclobutenamides **11** and **12**, respectively.[2–5] However, all attempts to isolate these latter compounds were unsuccessful. Although the reactions were conducted under anhydrous conditions, the crude products were exposed to air upon work-up and traces of water were probably sufficient to promote the hydrolysis of these strained species. An acidic aqueous work-up has also been used occasionally and comparable results were obtained. Thus, protonation of the enamide moiety in compound **11** would generate an α-aza-cyclobutyl cation, which could be attacked by hydroxide (or water) and give rise to hemiaminal **13**, which is in equilibrium with cyclobutanone **6**. Protonation of the enamide moiety of the trimethylsilyl-cyclobutenamide **12** would generate a cation stabilized by the nitrogen atom and the β-effect of silicon.[13] After Peterson type elimination, with formation of trimethylsilanol, the intermediate cyclobutenamide **11** would be generated and then ultimately converted to cyclobutanone **6** (Scheme 5).[14]

We have indeed observed that the gold-catalyzed cycloisomerization of ene-ynamide **8** could be carried out in CH_2Cl_2 containing D_2O [AuCl (10 mol %), D_2O (25 equiv), CH_2Cl_2, rt] and led to the *gem*-dideuteriated cyclobutanone **6′** (52%, >95% D_2) (Scheme 6).



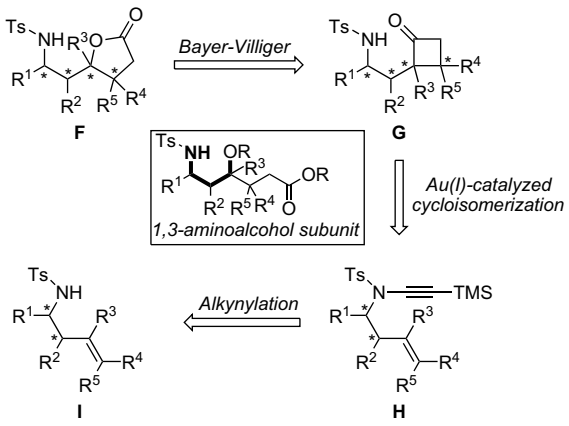
Scheme 5.



Scheme 6.

Though the mechanism of the gold-catalyzed reaction of ene-ynamides was not established unambiguously, the main difference compared to the platinum-catalyzed process would be that cyclobutenamides **11** and **12** did not undergo electrocyclic ring-opening due to the milder reaction conditions. An important consequence is that the stereogenic center (depicted with an asterisk on Scheme 5), initially created during the cycloisomerization process in intermediates **11** and **12**, is still present in the final cyclobutanone **6**. Controlling the configuration of this stereocenter would be interesting as cyclobutanones can be involved in stereospecific reactions such as, for example, the Baeyer–Villiger rearrangement leading to γ-lactones.

Thus, a variety of substituted γ-lactones of type **F**, which contain an interesting 1,3-aminoalcohol subunit, could be prepared by the Baeyer–Villiger oxidation of the corresponding cyclobutanones of type **G** that would be synthesized by gold-catalyzed cycloisomerizations of 1,6-ene-ynamides of type **H**. An important issue in these studies was to examine the possibility of achieving 1,3- or 1,2-stereochemical induction in the case of substrates bearing a stereogenic center at the α or β position of the nitrogen atom (R^1 or $R^2 \neq H$), respectively. Additionally, the creation of a quaternary center ($R^3 \neq H$) or an additional stereocenter (R^4 or $R^5 \neq H$) on the ring of γ-lactones **F** and cyclobutanones **G** would be feasible starting from 1,6-ene-ynamides of type **H** possessing a di-substituted alkene (R^3 or R^4 or $R^5 \neq H$). The 1,6-ene-ynamides of type **H** should be easily prepared by alkynylation of the corresponding sulfonamides **I** (Scheme 7).

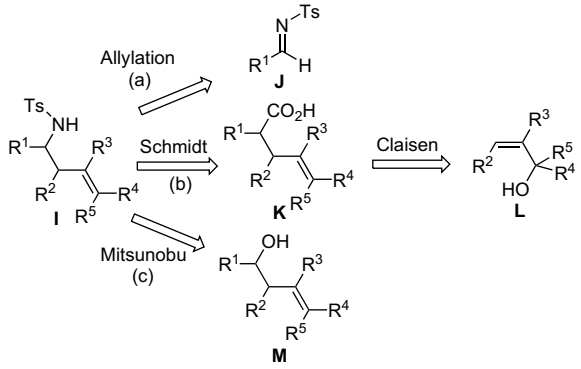


Scheme 7.

2.2. Diastereoselective cycloisomerizations of 1,6-ene-ynamides

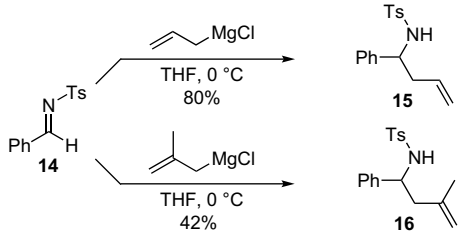
2.2.1. Preparation of the substrates

Three routes have been used to prepare sulfonamides **I**. The first one (route a) relies on the addition of an allylic organometallic reagent to a *N*-tosylaldimine **J**. The second route (route b) involves the formation of sulfonamides **I** from the corresponding primary amines generated by a Schmidt reaction applied to carboxylic acids of type **K**. The latter would be prepared from allylic alcohols **L** by a Claisen rearrangement. Finally, sulfonamides **I** can also be synthesized from homoallylic alcohols of type **M** by a Mitsunobu reaction utilizing a nitrogen nucleophile (route c) (Scheme 8).



Scheme 8.

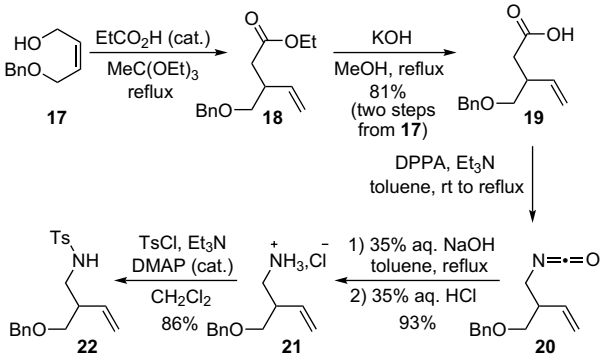
Two sulfonamides substituted at the α position of the nitrogen atom were first prepared. Treatment of *N*-tosylbenzaldimine **14** with allylmagnesium chloride or methallylmagnesium chloride (THF, 0 °C) provided the homoallylic sulfonamides **15** (80%) and **16** (42%), respectively (Scheme 9).



Scheme 9.

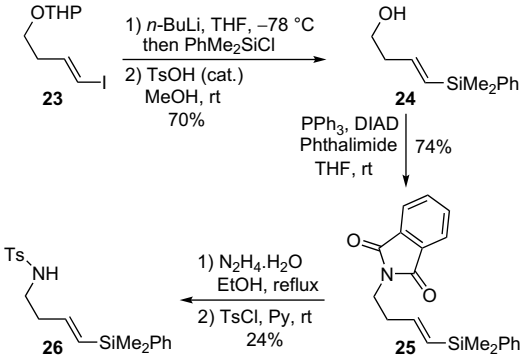
A sulfonamide possessing a stereogenic center at the β position of the nitrogen atom was prepared from allylic alcohol **17**. A Johnson–Claisen rearrangement [$EtCO_2H$ (cat.), $MeC(OEt)_3$, reflux] led to ethyl ester **18**,[15] which was saponified to afford the crude carboxylic acid **19** (81%, two steps from **17**). The latter compound underwent a Schmidt reaction [$(PhO)_2P(=O)N_3$ (DPPA), Et_3N, toluene, rt to reflux][16] and the resulting isocyanate **20** was hydrolyzed in situ by heating at reflux in the presence of 35% aq NaOH. After acidification (35% aq HCl), the crude hydrochloride **21** was isolated (93%). The nitrogen atom was then tosylated [TsCl, DMAP (cat.), Et_3N, CH_2Cl_2,

rt] to provide sulfonamide **22** (86%) bearing a benzyloxymethyl group substituent at the allylic position (Scheme 10).



Scheme 10.

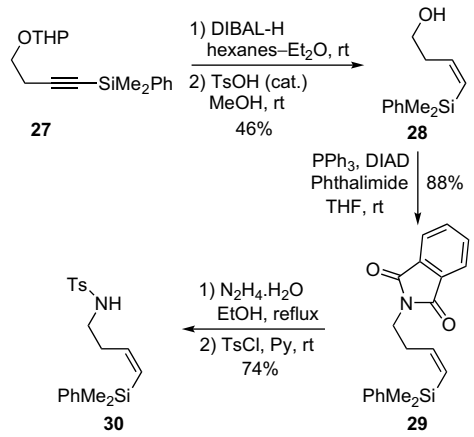
The synthesis of 1,6-ene-ynamides bearing an α,β-disubstituted double bond of defined configuration was then examined. It was envisaged to synthesize substrates bearing a dimethylphenylsilyl group as this substituent could later be transformed to a hydroxyl group by oxidation of the carbon–silicon bond.[17] The (*E*)-alkenyl iodide **23**[18] underwent lithium–iodine exchange (*n*-BuLi, THF, −78 °C) and the resulting alkenyllithium was silylated with $PhMe_2SiCl$ to afford, after cleavage of the THP ether [TsOH (cat.), MeOH, rt], the homoallylic alcohol **24** bearing a (*E*)-alkenyl silane (70%, two steps from **23**).[19] A Mitsunobu reaction with phthalimide [PPh_3, diisopropyl azodicarboxylate (DIAD), THF, rt] led to imide **25**, which underwent hydrazinolysis followed by tosylation of the resulting amine [TsCl, pyridine (Py), rt] to provide sulfonamide **26** in 24% unoptimized yield (two steps from **25**) (Scheme 11).



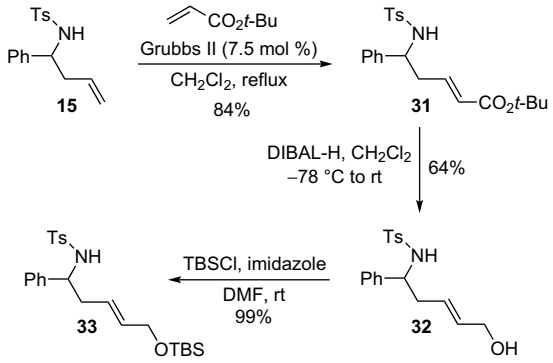
Scheme 11.

The isomeric sulfonamide bearing a (*Z*)-alkenyl silane was synthesized from alkynylsilane **27**.[20] After hydroalumination with DIBAL-H (hexanes/Et_2O, 0 °C to rt)[21] and subsequent cleavage of the THP ether, the (*Z*)-homoallylic alcohol **28** was obtained (46%, two steps from **27**).[20] The latter compound was converted to the homoallylic sulfonamide **30** as described previously (65%, three steps from **28**) (Scheme 12).

Finally, a sulfonamide possessing an α,β-disubstituted alkene and a stereogenic center at the α position of the nitrogen atom was prepared from the homoallylic sulfonamide **15**. A cross-metathesis with *tert*-butyl acrylate [Grubbs II catalyst (7.5 mol %), CH_2Cl_2, reflux] led to the α,β-unsaturated ester **31** (84%) as a single (*E*)-isomer.[22] Reduction of ester **31** to alcohol **32** (DIBAL-H, CH_2Cl_2, −78 °C to rt, 64%) followed by protection of the hydroxyl group as a *tert*-butyldimethylsilyl ether (TBSCl, imidazole, DMF, rt) provided the homoallylic sulfonamide **33** (99%) (Scheme 13).



Scheme 12.



Scheme 13.

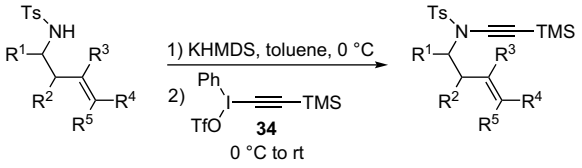
Having synthesized several homoallylic sulfonamides of type **I**, their conversion to the corresponding 1,6-ene-ynamides **H** was achieved by metalation with KHMDS (toluene, 0 °C) followed by alkynylation with (trimethylsilylethynyl)phenyliodonium triflate (**34**)[23] (toluene, 0 °C to rt) to provide compounds **35**–**40** in moderate to good yields (48–86%) (Table 1).[24]

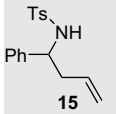
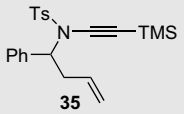
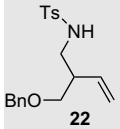
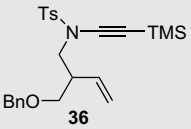
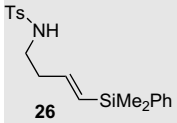
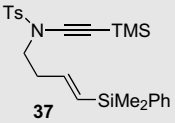
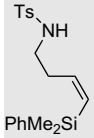
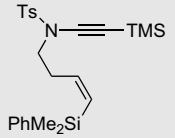
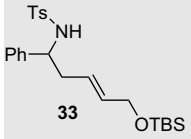
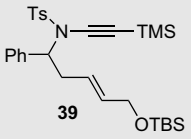
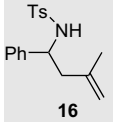
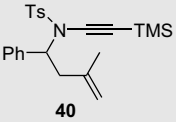
The gold-catalyzed cycloisomerizations of these 1,6-ene-ynamides could then be investigated and an important goal was to determine whether efficient levels of 1,3- or 1,2-stereochemical induction could be observed for substrates bearing a stereogenic center at the α or β position of the nitrogen atom, respectively.

2.2.2. Gold-catalyzed cycloisomerizations of 1,6-ene-ynamides bearing substituents at the α or β position of the nitrogen atom

2.2.2.1. Cycloisomerization reactions. At first, the 1,3-stereochemical induction was examined. Thus, ene-ynamide **35** was treated with a catalytic amount of AuCl [(5–10 mol %), CH_2Cl_2, rt]. A slow reaction took place (24–48 h) and analysis of the ^1H NMR spectrum of the crude material indicated the formation of cyclobutanone **41** with high diastereoselectivity (dr >95:5).[25] However, a slight erosion of the diastereomeric purity was observed after purification by flash chromatography on silica gel since cyclobutanone **41** was isolated as an 88:12 mixture of epimers (77%).[26] To confirm this result, the crude cyclobutanone **41** was not purified but directly subjected to a Baeyer–Villiger reaction.[12] Under these conditions, the γ-lactone **42** was obtained with high diastereoselectivity (dr >95:5) and isolated in 65% yield (two steps from 1,6-ene-ynamide **35**). The relative configuration of γ-lactone **42**, and hence the one of cyclobutanone **41** from which it has been obtained by a stereospecific Baeyer–Villiger reaction (retention of configuration at the migrating center),[12] was ascertained by chemical correlation (see

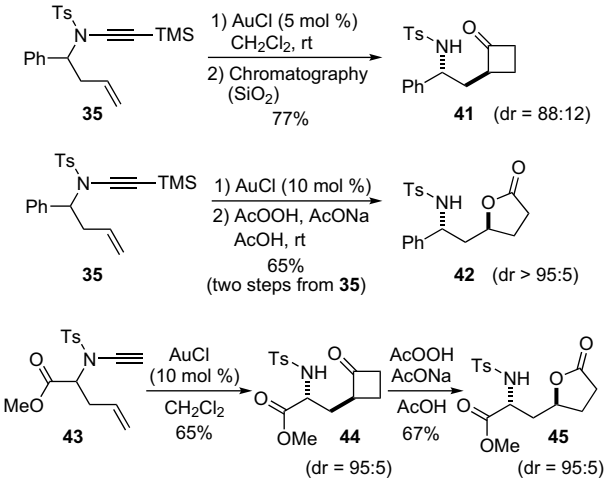
Table 1
Preparation of substituted 1,6-ene-ynamides **H**



Sulfonamides **I**	Ynamides **H**	Yield (%)
 **15**	 **35**	60
 **22**	 **36**	63
 **26**	 **37**	48
 **30**	 **38**	86
 **33**	 **39**	50
 **16**	 **40**	67

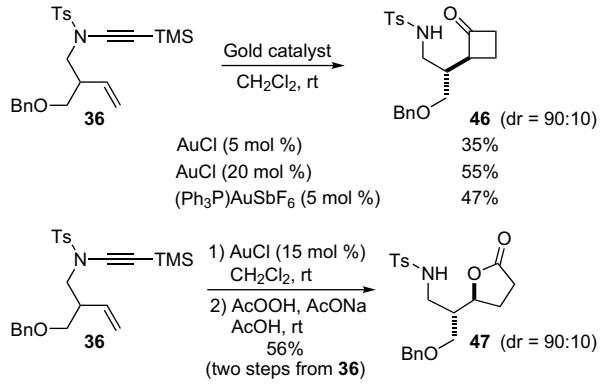
Section 4.6.3). The observed sense of 1,3-stereochemical induction in the gold-catalyzed cycloisomerizations of 1,6-ene-ynamides substituted at the α position of the nitrogen atom was also later confirmed with substrates bearing a propargylic alcohol (Section 2.3.2). To highlight the functional group tolerance of the gold-catalyzed cycloisomerizations, the known terminal ene-ynamide **43** was also prepared[27] and treated with a catalytic amount of AuCl [(10 mol %), CH_2Cl_2, rt]. Cyclobutanone **44** was obtained with high diastereoselectivity (dr=95:5) and isolated in 65% yield. Subsequent Baeyer–Villiger oxidation of cyclobutanone **44** provided the functionalized γ-lactone **45** (67%). This result confirmed the high diastereoselectivity of the gold-catalyzed cycloisomerization of ene-ynamides bearing a stereogenic center at the α position of the-nitrogen atom whatever the substituent (Ph or CO_2Me) (Scheme 14).

In order to evaluate the 1,2-stereochemical induction, the gold-catalyzed cycloisomerization of ene-ynamide **36**, bearing a stereocenter at the β position of the nitrogen, was investigated. A slow reaction was observed under standard conditions [AuCl (5 mol %), CH_2Cl_2, rt, 48 h] and cyclobutanone **46** was isolated in low yield (35%). The steric hindrance around the olefinic moiety may slow down its attack on the ynamide activated by the gold catalyst. Increasing the loading of AuCl (20 mol %) or the use of the more



Scheme 14.

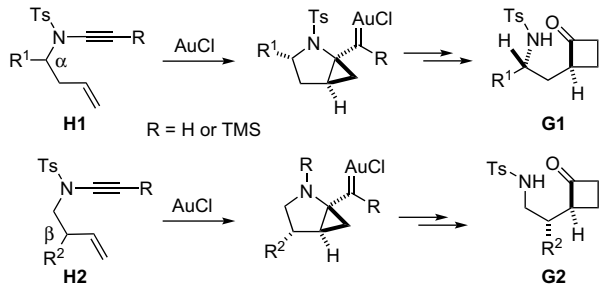
reactive catalyst $(Ph_3P)AuSbF_6$ [generated from $(Ph_3P)AuCl$ (5 mol %) and $AgSbF_6$ (5 mol %)] enabled to improve the isolated yields of cyclobutanone **46** (55% and 47%, respectively).[28] The observed diastereoselectivity was satisfactory (dr=90:10) although slightly lower than for substrates substituted at the α position of the nitrogen atom. Finally, a gold-catalyzed cycloisomerization and Baeyer–Villiger oxidation two-step sequence, without purification of the intermediate cyclobutanone **46**, afforded γ-lactone **47** in 56% overall yield (Scheme 15).



Scheme 15.

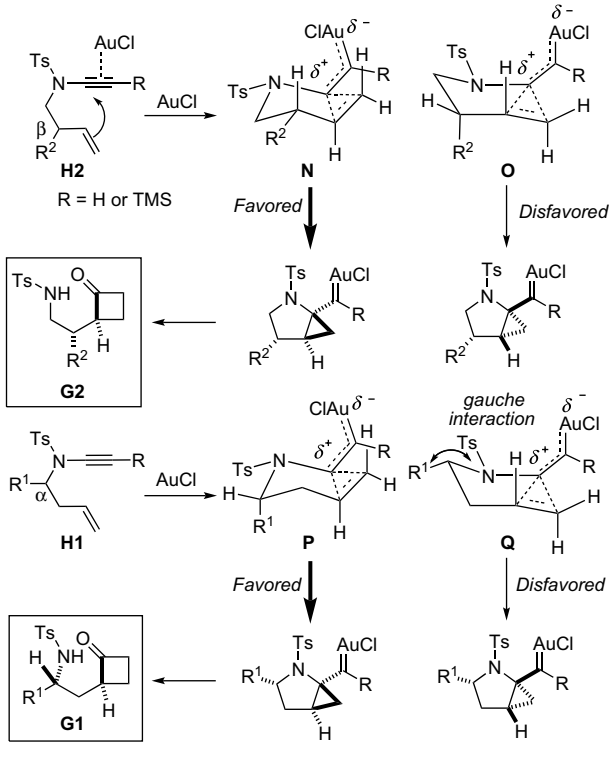
Thus, the gold-catalyzed cycloisomerizations of substituted 1,6-ene-ynamides occurred with synthetically useful levels of diastereoselectivity (dr=90:10 to >95:5). The observed sense of 1,3- and 1,2-induction in the case of 1,6-ene-ynamides of type **H1** and **H2**, respectively, indicates that the three-membered ring in the gold cyclopropylcarbene intermediates is predominantly formed *anti* to the substituent on the chain, leading after ring-expansion, demetalation, and hydrolysis to cyclobutanone of type **G1** and **G2** (Scheme 16).

2.2.2.2. Interpretation of the diastereoselectivity. The formation of the different possible products in the noble metal-catalyzed cycloisomerization of ene-ynes has been well rationalized on the basis of mechanisms involving metal cyclopropylcarbene intermediates.[3,4] Nevertheless, as pointed out in a recent article, the reactive intermediates in the gold-catalyzed cycloisomerization of enynes should rather be considered as gold-stabilized carbocations.[29] To explain the diastereoselectivity of the gold-catalyzed reactions of substituted 1,6-ene-ynamides, we indeed considered



Scheme 16.

an analogy with cationic cyclizations involving *N*-acyliminium ions.[30] Thus, a cyclic chair-like transition state may be considered wherein a π-complex is formed between the alkene and the developing nitrogen-stabilized vinylic carbocation, generated upon coordination of the gold catalyst to the alkyne. Thus, for 1,6-ene-ynamides **H2** bearing a substituent at the β position of the nitrogen atom, cyclization should occur faster through the reactive conformer **N** compared to **O**, as the R^2 substituent should preferentially occupy a pseudo-equatorial position. This hypothesis would effectively explain the formation of cyclobutanones **G2** as the major diastereomers. For 1,6-ene-ynamides **H1** bearing a substituent at the α position of the nitrogen atom, the diastereoselective formation of cyclobutanones of type **G1** suggested that cyclization should be faster through the reactive conformer **P** than through conformer **Q**. This result is in agreement with the literature precedents on cationic cyclization involving *N*-acyliminium cations.[30] Indeed, the R^1 substituent should preferentially occupy an axial position in the cyclic transition state to avoid a severe *gauche* interaction with the substituent on the nitrogen atom (tosyl group). Stabilization of the developing carbocation by the nitrogen should further enhance this interaction, which becomes similar to $A^{1,2}$ strain (Scheme 17).

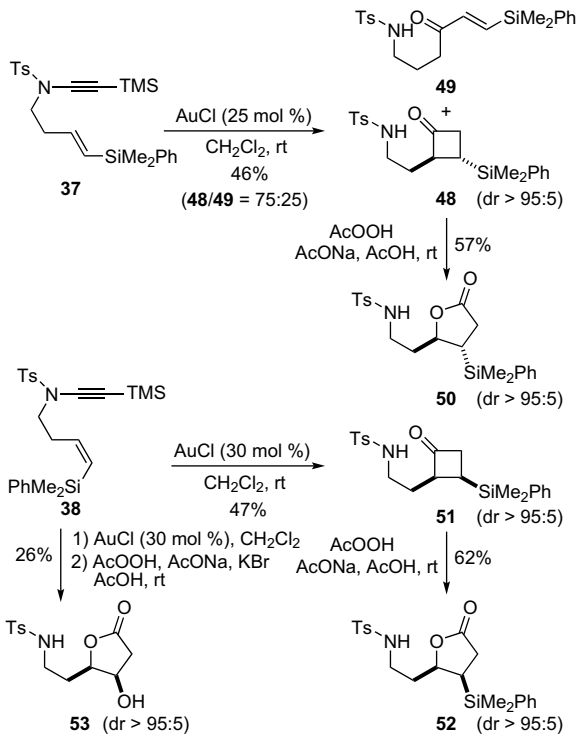


Scheme 17.

The cycloisomerizations of 1,6-ene-ynamides bearing a disubstituted alkene was next investigated.

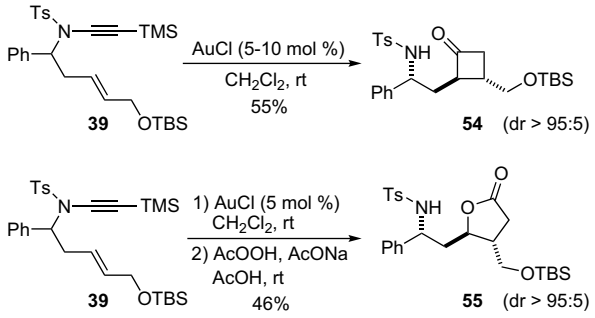
2.2.3. *Cycloisomerizations of 1,6-ene-ynamides possessing a disubstituted alkene*

The gold-catalyzed cycloisomerization of ene-ynamides **37** and **38**, bearing a (*E*)- or a (*Z*)-alkenyl silane, respectively, was then studied. A high catalyst loading [AuCl (25–30 mol %), CH_2Cl_2, rt] was required for those substrates due to the steric hindrance brought by the phenyldimethylsilyl group. Side-products were also formed but their structure could not be unambiguously determined. Under those conditions, ynamide **37** led to a 75:25 inseparable mixture of the expected cyclobutanone **48** and the β-silylenone **49** (46%).[31] The cycloisomerization of ynamide **38**, possessing a (*Z*)-alkenyl silane, produced cyclobutanone **51** in 47% yield. Cyclobutanones **48** and **51** were obtained in each reaction with high diastereoselectivity (dr >95:5), indicating that the gold-catalyzed cycloisomerization involves a stereospecific process. The Baeyer–Villiger oxidation of cyclobutanones **48** and **51** led to the diastereomeric lactones **50** (57%) and **52** (62%), respectively, whose relative configurations were ascertained by a chemical correlation (see Section 4.6.3). Additionally, the possibility of carrying out a gold-catalyzed cycloisomerization followed by one-pot Baeyer–Villiger and Tamao–Fleming oxidation reactions[17] was examined with ene-ynamide **38**. This could be achieved by simply adding KBr in the presence of AcOOH during the oxidation step[17] and the β-hydroxy-γ-substituted lactone **53** was obtained (26%) but no attempt was made to improve the overall yield of this sequence (Scheme 18).



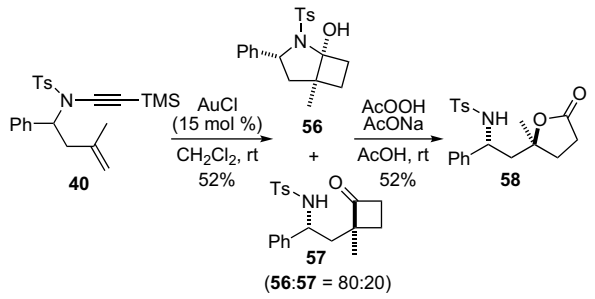
Scheme 18.

The cycloisomerization of ene-ynamide **39** bearing both a stereogenic center at the α position of the nitrogen atom and an α,β-disubstituted alkene proceeded smoothly by treatment with AuCl [(5–10 mol %), CH_2Cl_2, rt] and afforded cyclobutanone **54** as a single diastereomer (55%). When this compound was not purified but directly engaged in a Baeyer–Villiger oxidation, the corresponding disubstituted γ-lactone **55** was isolated (46%, two steps from **39**) (Scheme 19).



Scheme 19.

The gold-catalyzed cycloisomerization of ene-ynamide **40**, possessing an α,α-disubstituted alkene, was finally examined. The reaction led to an 80:20 equilibrium mixture of the bicyclic hemiaminal **56** and the cyclobutanone **57** (single diastereomers, 52%). It is worth noting that the formation of bicyclic hemiaminals was also observed in some platinum-catalyzed cycloisomerizations of 1,7-ene-ynamides bearing an α,α-disubstituted double bond.[8] The Baeyer–Villiger oxidation of the mixture of compounds **56** and **57** proceeded extremely slowly and afforded γ-lactone **58** in modest yield (52%) (Scheme 20).



Scheme 20.

Thus, the gold-catalyzed cycloisomerization of 1,6-ene-ynamides bearing substituents on the alkene can lead to cyclobutanones and γ-lactones possessing a quaternary center.

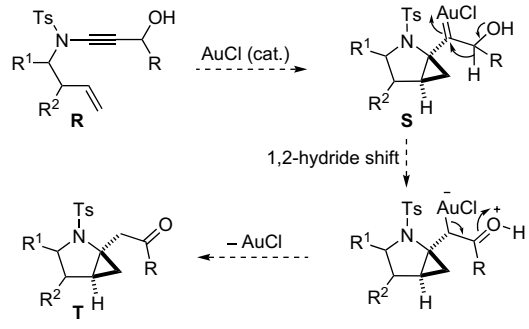
2.3. Cycloisomerizations of 1,6-ene-ynamides possessing a propargylic alcohol moiety

In the preceding examples of gold-catalyzed cycloisomerization of ene-ynamides, the putative intermediate cyclobutenamides, that may have potentially been interesting building blocks for the formation of nitrogen heterocycles, could not be isolated due to their sensitivity toward moisture. The key reactive intermediate in the gold-catalyzed cycloisomerization of ene-ynamides contains a substituted 2,3-methanopyrrolidine subunit that would be interesting to keep in the final products. The reactivity of 1,6-ene-ynamides of type **R** bearing a propargylic alcohol moiety was thus examined. For those substrates, by analogy with the behavior of non-heterosubstituted enynes bearing a propargylic alcohol moiety,[4j] the corresponding gold cyclopropylcarbenes **S** should undergo a rapid 1,2-hydride shift leading, after demetalation, to carbonyl compounds of type **T** bearing a 2,3-methanopyrrolidine subunit (Scheme 21).

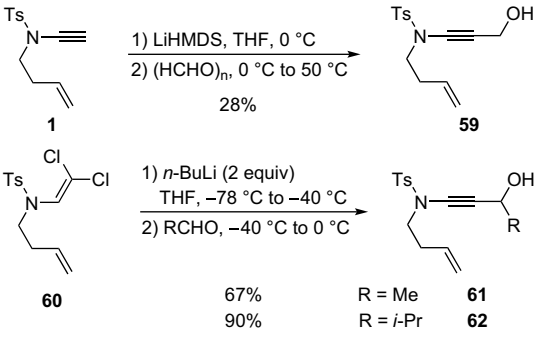
Thus, the preparation of ene-ynamides of type **R** was carried out to examine their reactivity in the presence of gold catalysts.

2.3.1. Preparation of the substrates

The simplest route toward ene-ynamides of type **R** appeared to involve the functionalization of a lithium alkynylide derived from a terminal ynamide. However, metalation of ynamide **1** with LiHMDS (THF, 0 °C) followed by addition of paraformaldehyde (0–50 °C) led to the disubstituted ynamide **59** in low yield (28%). Indeed, direct metalation of terminal ynamides is not efficient for the generation of the corresponding lithium alkynylides[32] but generation of such species is best achieved by treatment of *N*-(β,β-dichlorovinyl)enamides with *n*-BuLi (2 equiv, THF, −78 °C to −40 °C).[32,33] These conditions were applied to β,β-dichloro-enamide **60** and after addition of acetaldehyde or isobutyraldehyde, the secondary propargylic alcohols **61** (67%) and **62** (90%) were obtained, respectively (Scheme 22).



Scheme 21.



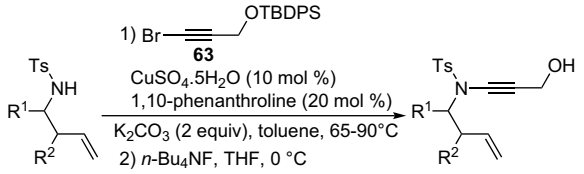
Scheme 22.

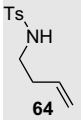
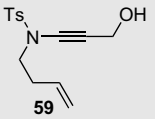
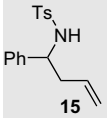
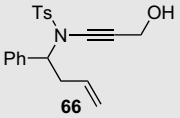
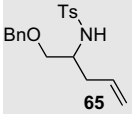
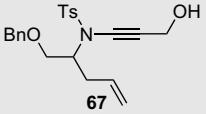
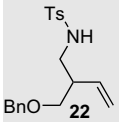
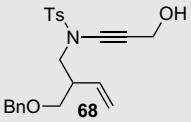
A straightforward access to ene-ynamides of type **R** was also achieved by a copper-catalyzed cross-coupling between various sulfonamides[34] and bromoalkyne **63** derived from propargyl alcohol [$CuSO_4 \cdot 5H_2O$ (10 mol %), 1,10-phenanthroline (20 mol %), K_2CO_3, toluene, 65–90 °C].[35,36] The corresponding disubstituted ynamides underwent subsequent deprotection of the alcohol (*n*-Bu_4NF, THF, 0 °C) to afford the 1,6-ene-ynamides **59**, **66**–**68**, bearing a propargylic alcohol moiety (28–87% overall yield) (Table 2).

2.3.2. Cycloisomerization reactions

The ene-ynamide **59**, bearing a primary propargylic alcohol, reacted rapidly in the presence of AuCl [(5 mol %), CH_2Cl_2, rt] and afforded aldehyde **69** (40%), possessing a 2,3-methanopyrrolidine subunit. The ene-ynamides **61** and **62**, bearing a secondary propargylic alcohol, also led to clean reactions and the corresponding ketones **70** and **71** were isolated in 60% and 42% yield, respectively. As expected, the gold-catalyzed cycloisomerization of 1,6-ene-ynamides **66** and **67**, substituted at the α position of the nitrogen atom, proceeded with high diastereoselectivity (dr >95:5) and provided aldehydes **72** (61%) and **73** (51%). In agreement with the results observed for the related trimethylsilyl ene-ynamides, ene-ynamide **68**, which is substituted at the β position of the nitrogen atom, underwent a gold-catalyzed cycloisomerization with a slightly lower but appreciable level of diastereoselection

Table 2
Preparation of ynamides of type **R**



Sulfonamides	Ene-ynamides **R**	Yield (%)
 **64**	 **59**	66
 **15**	 **66**	55
 **65**	 **67**	28
 **22**	 **68**	87

(dr=90:10). The resulting aldehyde, which partially decomposed when purification by chromatography on silica gel was attempted, was immediately reduced ($NaBH_4$, MeOH, rt) to provide the primary alcohol **74** in 60% yield. The relative configuration of compounds **72** and **74** was unambiguously ascertained by NMR (NOESY correlations, see Section 4.8) (Table 3).

3. Conclusion

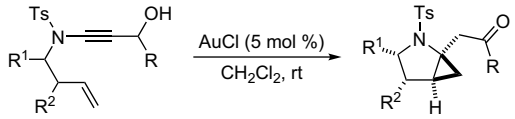
The gold-catalyzed cycloisomerizations of 1,6-ene-ynamides can provide access to cyclobutanones if the ynamide is terminal or substituted by a trimethylsilyl group. Alternatively, from ynamides possessing a propargylic alcohol moiety, aldehydes or ketones bearing a 2,3-methanopyrrolidine subunit can be efficiently synthesized. Particularly noteworthy are the high 1,3- or 1,2-diastereoselectivities observed with substrates bearing a stereocenter at the α or β position of the nitrogen atom.

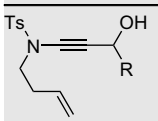
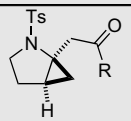
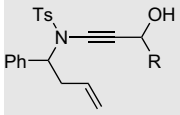
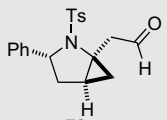
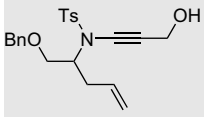
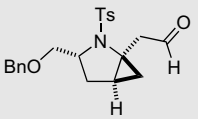
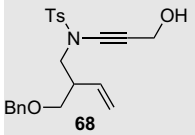
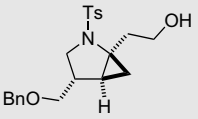
4. Experimental section

4.1. General procedures

Infrared (IR) spectra were recorded on a Bruker Tensor 27 (IR-FT), wavenumbers are indicated in cm^{-1}. ^1H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) and data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or overlap of non-equivalent resonances), integration. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 or 100 MHz and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$, δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s=quaternary C, d=CH, t=CH_2, q=CH_3). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett–Packard tandem 5890A GC (12 m capillary column)—5971 MS (70 eV). THF and diethyl ether were distilled from sodium/benzophenone. CH_2Cl_2, CH_3CN, toluene, Et_3N, i-Pr_2NH were distilled from CaH_2. Other reagents were obtained from commercial suppliers and used as received. TLC was performed on silica gel plates and visualized either with a UV lamp (254 nm), or by using solutions of p-anisaldehyde/H_2SO_4/AcOH in EtOH or $KMnO_4/K_2CO_3$ in water followed by heating. Flash chromatography was performed on silica gel (230–400 mesh).

Table 3
Gold-catalyzed cycloisomerization of ene-ynamides of type **R**



Ene-ynamides **R**	Products	Yield (%)
		
59 R=H	**69** R=H	40
61 R=Me	**70** R=Me	60
62 R=*i*-Pr	**71** R=*i*-Pr	42
 **66**	 **72**	61
 **67**	 **73**	51
 **68**	 **74**[a]	60[a]

[a] The intermediate aldehyde was reduced ($NaBH_4$, MeOH, rt).

4.2. Preliminary investigations

The terminal ene-ynamides **1** and **3** were synthesized as described in the literature,[8,9] whereas the trimethylsilyl ene-ynamides **8** and **9** were prepared by alkynylation of the corresponding sulfonamides.

*4.2.1. N-(But-3-enyl)-4-methyl-N-(trimethylsilylethynyl)-benzenesulfonamide (**8**)*

To a solution of *N*-(but-3-enyl)-4-methylbenzenesulfonamide[8,9] (3.08 g, 13.7 mmol) in toluene (150 mL) at 0 °C was added KHMDS (30.2 mL, 0.5 M in toluene, 15.1 mmol, 1.1 equiv). After 2 h at 0 °C, (trimethylsilylethynyl)phenyliodonium triflate (**34**) (7.40 g, 16.4 mmol, 1.2 equiv) was added portionwise. After 24 h at rt, the reaction mixture was filtered through Celite (toluene/Et_2O: 80:20). The filtrate was evaporated under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/EtOAc 95:5, 90:10) to afford 3.43 g (78%) of **8** as a pale yellow solid. ($C_{16}H_{23}NO_2SSi$, MW=321.51 g mol^{-1}). Mp 53–55 °C; IR 2155, 1590,

1365, 1245, 1165, 1085, 910, 840, 755, 730, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 5.70 (ddt, J=16.9, 10.3, 6.6 Hz, 1H), 5.08 (dq, J=16.9, 1.5 Hz, 1H), 5.03 (dq, J=10.3, 1.5 Hz, 1H), 3.36 (t, J=7.4 Hz, 2H), 2.45 (s, 3H), 2.41–2.33 (m, 2H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.5 (s), 134.5 (s), 133.6 (d), 129.5 (d, 2C), 128.1 (d, 2C), 117.5 (t), 94.8 (s), 73.5 (s), 50.5 (t), 32.0 (t), 21.5 (q), 0.0 (q, 3C); MS-EI m/z (relative intensity) 321 (M^+, 1), 256 (29), 166 (77), 164 (23), 155 (30), 150 (22), 149 (33), 139 (25), 110 (37), 91 (77), 84 (23), 73 (100), 59 (29), 55 (29). Anal. Calcd for $C_{16}H_{23}NO_2SSi$: C, 59.77; H, 7.21; N, 4.36. Found: C, 59.81; H, 7.37; N, 4.28.

4.2.2. Benzyl N-(but-3-enyl)-N-(trimethylsilylethynyl)-carbamate (**9**)

To a solution of benzyl *N*-(but-3-enyl)carbamate[37] (731 mg, 3.61 mmol) in toluene (45 mL) at 0 °C was added KHMDS (8.54 mL, 0.5 M in toluene, 4.27 mmol, 1.2 equiv). After 1 h at 0 °C, (trimethyl silylethynyl)phenyliodonium triflate (**34**) (2.11 g, 4.69 mmol, 1.3 equiv) was added. After 24 h at rt, the reaction mixture was filtered through Celite (toluene/Et_2O 80:20). The filtrate was evaporated under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/EtOAc gradient 98:2 to 90:10) to afford 120 mg (11%) of **9** as a yellow oil ($C_{17}H_{23}NO_2Si$, MW=301.46 g mol^{-1}). IR 2174, 1726, 1642, 1391, 1275, 1248, 1210, 1149, 916, 838, 757, 734, 695, 616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41–7.30 (m, 5H), 5.78 (ddt, J=17.1, 10.2, 6.9 Hz, 1H), 5.22 (s, 2H), 5.13 (dd, J=17.1, 1.3 Hz, 1H), 5.06 (br d, J=10.2 Hz, 1H), 3.78 (t, J=7.2 Hz, 2H), 2.44 (td, apparent q, J=7.0 Hz, 2H), 0.19 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.2 (s), 135.6 (s), 134.1 (d), 128.4 (d, 2C), 128.0 (d, 2C), 127.3 (d), 117.4 (t), 95.3 (s), 72.8 (s), 68.2 (t), 48.9 (t), 31.9 (t), 0.15 (q, 3C); MS-EI m/z (relative intensity) 301 (M^+, 1), 256 (6), 242 (5), 184 (4), 168 (4), 167 (14), 110 (6), 92 (9), 91 (100), 73 (8), 65 (6), 55 (4). Anal. Calcd for $C_{17}H_{23}NO_2Si$: C, 67.73; H, 7.69; N, 4.65. Found: C, 67.67; H, 7.51; N, 4.62.

4.2.3. 4-Methyl-N-[2-(2-oxocyclobutyl)ethyl]benzene-sulfonamide (**6**)

To a solution of ynamide **1** (90 mg, 0.36 mmol) in CH_2Cl_2 (3 mL) was added AuCl (4 mg, 0.02 mmol, 0.05 equiv). After 1 h at rt, the reaction mixture was filtered through Celite (CH_2Cl_2) and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc 70:30+0.5% Et_3N) to afford 48 mg (50%) of **6** as a pale yellow oil. This compound can also be prepared from the trimethylsilyl-1,6-ene-ynamide **8** (100 mg, 0.311 mmol) by treatment with AuCl (3.8 mg, 0.016 mmol, 0.05 equiv) in CH_2Cl_2 (3 mL) (16 h, rt). After the same work-up as described above, purification by flash chromatography (petroleum ether/EtOAc 70:30+0.5% Et_3N), 53 mg (61%) of **6** was obtained as a yellow oil. Compound **6** was obtained in similar yield if a hydrolytic work-up with a 1 M solution of hydrochloric was used, followed by extraction (EtOAc) and drying ($MgSO_4$) ($C_{13}H_{17}NO_3S$, MW=267.34 g mol^{-1}). IR 3278, 1773, 1598, 1428, 1325, 1156, 1091, 816, 662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (d, J=8.3 Hz, 2H), 7.30 (d, J=8.3 Hz, 2H), 5.17 (br t, J=6.0 Hz, 1H, NH), 3.33–3.22 (m, 1H), 3.14–3.00 (m, 2H), 2.98–2.84 (m, 2H), 2.43 (s, 3H), 2.19 (dddd, apparent qd, J=10.7, 4.8 Hz, 1H), 1.83–1.67 (m, 2H), 1.66–1.57 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 211.5 (s), 143.3 (s), 137.0 (s), 129.7 (d, 2C), 127.0 (d, 2C), 58.2 (d), 44.3 (t), 41.4 (t), 29.4 (t), 21.5 (q), 16.5 (t); MS-EI m/z (relative intensity) 239 ($M-C_2H_4^+$, 29), 184 (50), 157 (6), 156 (9), 155 (100), 132 (8), 112 (13), 92 (10), 91 (86), 77 (9), 65 (19), 55 (10).

4.2.4. 4-Methyl-N-[2-(3,3-dideuterio-2-oxocyclobutyl)-ethyl]benzenesulfonamide (**6′**)

To a solution of ynamide **8** (78 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) were added D_2O (110 μL, 6.0 mmol, 25 equiv) and AuCl (5.6 mg, 0.024 mmol, 0.1 equiv). After 3 h of vigorous stirring at rt, the reaction mixture was diluted with EtOAc and H_2O, the layers were separated, and the aqueous phase was extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by preparative TLC on a silica gel plate (pentane/EtOAc 60:40) to afford 34 mg (52%) of **6′** as a colorless oil ($C_{13}H_{15}D_2NO_3S$, MW=269.36 g mol^{-1}). ^1H NMR ($CDCl_3$) δ 7.74 (d, J=8.3 Hz, 2H), 7.30 (d, J=8.3 Hz, 2H), 5.17 (br t, J=6.0 Hz, 1H, NH), 3.27 (dddd, apparent dq, J=10.7, 7.9 Hz, 1H), 3.14–3.06 (m, 1H), 2.98–2.89 (m, 1H), 2.43 (s, 3H), 2.19 (dd, apparent br t, J=10.7 Hz, 1H), 1.83–1.67 (m, 2H), 1.62–1.58 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 211.5 (s), 143.3 (s), 137.0 (s), 129.7 (d, 2C), 127.0 (d, 2C), 58.2 (d), 44.1 (CD_2, barely visible signal), 41.4 (t), 29.4 (t), 21.5 (q), 16.5 (t).

4.2.5. 4-Methyl-N-[2-(5-oxotetrahydrofuran-2-yl)ethyl]-benzenesulfonamide (**7**)

To a solution of cyclobutanone **6** (110 mg, 0.412 mmol) in AcOH (3 mL) were added $AcONa\cdot 3H_2O$ (67 mg, 0.49 mmol, 1.2 equiv) and a solution of AcOOH (0.35 mL, 32% in AcOH, 1.6 mmol, 4 equiv). After 2 h at rt, the reaction mixture was cooled in an ice-bath and hydrolyzed with a 25% aqueous solution of $Na_2S_2O_3$. After addition of water and extraction with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient 50:50 to 30:70) to afford 89 mg (77%) of **7** as a viscous colorless oil ($C_{13}H_{17}NO_4S$, MW=283.34 g mol^{-1}). IR 3265, 1760, 1597, 1324, 1189, 1152, 1091, 1069, 917, 814, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (d, J=8.1 Hz, 2H), 7.30 (d, J=8.1 Hz, 2H), 5.46 (t, J=6.2 Hz, 1H, NH), 4.55 (m, 1H), 3.10–3.02 (m, 2H), 2.52–2.48 (m, 2H), 2.42 (s, 3H), 2.36–2.30 (m, 1H), 1.90–1.78 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 177.0 (s), 143.4 (s), 136.4 (s), 129.7 (d, 2C), 126.9 (d, 2C), 78.4 (d), 39.8 (t), 35.4 (t), 28.5 (t), 27.8 (t), 21.5 (q); MS-EI m/z (relative intensity) 283 (M^+, 14), 219 (4), 184 (57), 155 (100), 128 (13), 92 (9), 91 (82), 85 (11), 65 (17).

4.2.6. Benzyl N-[2-(2-oxocyclobutyl)ethyl]carbamate (**10**)

This compound was prepared by treatment of ynamide **9** (62 mg, 0.20 mmol) with AuCl (7 mg, 0.03 mmol, 0.15 equiv) in CH_2Cl_2 (3 mL). After 48 h at rt, work-up and purification by flash chromatography (petroleum ether/EtOAc gradient 80:20 to 70:30) gave 29 mg (59%) of **10** as a colorless oil ($C_{14}H_{17}NO_3$, MW=247.29 g mol^{-1}). IR 3337, 1773, 1698, 1525, 1454, 1242, 1135, 1088, 1026, 775, 735, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.27 (m, 5H), 5.21 (m, apparent br s, 1H, NH), 5.09 (br s, 2H), 3.37–3.26 (m, 2H), 3.24–3.16 (m, 1H), 3.10–3.00 (m, 1H), 2.95–2.86 (m, 1H), 2.21 (apparent qd, J=10.6, 5.0 Hz, 1H), 1.88–1.62 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 211.5 (s), 156.4 (s), 136.6 (s), 128.4 (2d, 3C), 128.0 (d, 2C), 66.5 (t), 58.3 (d), 44.4 (t), 39.1 (t), 29.7 (t), 16.7 (t); MS-EI m/z (relative intensity) 219 ($M-C_2H_4^+$, 1), 128 (6), 111 (25), 108 (30), 107 (20), 92 (9), 91 (100), 79 (28), 77 (18), 69 (5), 65 (8), 56 (12), 55 (26), 51 (7). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.89; H, 7.02; N, 5.57.

4.3. Preparation of sulfonamides of type I

4.3.1. 4-Methyl-N-(1-phenylbut-3-enyl)benzenesulfonamide (**15**)[37]

To a solution of *N*-tosylbenzaldimine (**14**)[38] (3.00 g, 11.6 mmol) in THF (20 mL) at −10 °C was added allylmagnesium chloride (8.70 mL, 2 M in THF, 17.4 mmol, 1.5 equiv). After 2 h at 0 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were successively washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) to afford 2.78 g (80%) of **15** as white crystals

($C_{17}H_{19}NO_2S$, MW=301.40 g mol^{-1}). Mp 77–78 °C; IR 3260, 1595, 1420, 1320, 1155, 915, 810, 700, 665 cm^{-1}; ^{1}H NMR δ 7.57 (d, J=8.5 Hz, 2H), 7.19–7.06 (m, 7H), 5.60–5.46 (m, 1H), 5.30 (d, J=7.0 Hz, 1H, NH), 5.08–5.01 (m, 2H), 4.38 (apparent q, J=7.0 Hz, 1H), 2.58–2.39 (m, 2H), 2.37 (s, 3H); ^{13}C NMR δ 143.0 (s), 140.4 (s), 137.5 (s), 133.1 (d), 129.3 (d, 2C), 128.3 (d, 2C), 127.3 (d), 127.1 (d, 2C), 126.6 (d, 2C), 119.0 (t), 57.3 (d), 41.8 (t), 21.4 (q); MS-EI m/z (relative intensity) 301 (M$^+$, 1), 261 (18), 260 (M−Allyl$^+$, 100), 155 (56), 91 (71).

4.3.2. 4-Methyl-N-(3-methyl-1-phenylbut-3-enyl)-benzenesulfonamide (**16**)

To a solution of *N*-tosylbenzaldimine (**14**)[38] (760 mg, 2.93 mmol) in THF (10 mL) at 0 °C was slowly added methallylmagnesium chloride (8.8 mL, 0.5 M in THF, 4.4 mmol, 1.5 equiv). After 1 h at 0 °C, another quantity of methallylmagnesium chloride (8.8 mL, 1.5 equiv) was added. After 1 h at 0 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were successively washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (toluene/*i*-PrOH 98:2) to afford 402 mg (43%) of **16** as white crystals ($C_{18}H_{21}NO_2S$, MW=315.43 g mol^{-1}). Mp 72 °C; IR 3251, 1652, 1598, 1494, 1440, 1415, 1320, 1303, 1289, 1155, 1085, 941, 891, 815, 757, 701, 667 cm^{-1}; ^{1}H NMR δ 7.52 (d, J=8.3 Hz, 2H), 7.20–7.09 (m, 7H), 4.87 (d, J=4.5 Hz, 1H, NH), 4.83 (apparent t, J=1.5 Hz, 1H), 4.73 (apparent br s, 1H), 4.37 (ddd, J=8.0, 7.0, 4.5 Hz, 1H), 2.40–2.33 (m, 2H), 2.36 (s, 3H), 1.52 (s, 3H); ^{13}C NMR δ 143.0 (s), 141.1 (s), 140.9 (s), 137.1 (s), 129.2 (d, 2C), 128.3 (d, 2C), 127.3 (d), 127.2 (d, 2C), 126.6 (d, 2C), 115.2 (t), 55.5 (d), 46.7 (t), 21.5 (q), 21.4 (q); MS-EI m/z (relative intensity) 261 (17), 260 (M−Methallyl$^+$, 100), 156 (5), 155 (56), 129 (6), 104 (8), 92 (6), 91 (71), 77 (7), 65 (10).

4.3.3. N-(2-Benzyloxymethylbut-3-enyl)-4-methyl-benzenesulfonamide (**22**)

To a solution of **17** (4.00 g, 22.4 mmol) in triethyl orthoacetate (20.4 mL, 112 mmol, 5 equiv) was added propionic acid (170 μL, 2.24 mmol, 0.1 equiv). The reaction mixture was slowly heated at 100 °C while EtOH was distilled off. The temperature was increased to 150 °C and after 2 h, the reaction mixture was concentrated under reduced pressure. The crude ester **18**[15] was dissolved in MeOH (25 mL) and KOH (2.52 g, 44.9 mmol, 2 equiv) was added. After 4 h heating at reflux, the reaction mixture was cooled to rt, diluted with H_2O, and extracted with Et_2O. The organic extracts were discarded and the aqueous phase was acidified (pH <1) by slow addition of 35% hydrochloric acid at 0 °C. After extraction with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 4.00 g (18.2 mmol) (81%) of the crude carboxylic acid **19** as a colorless oil, which was dissolved in toluene (100 mL). To the resulting solution at rt were added Et_3N (3.04 mL, 21.8 mmol, 1.2 equiv) and DPPA (4.3 mL, 20 mmol, 1.1 equiv). After 1 h at rt, the reaction mixture was heated at reflux for 2 h and cooled to rt. Half of the solvent was evaporated under reduced pressure and the resulting solution of isocyanate **20** was treated with a 30% aqueous solution of NaOH (15 mL). After 2 h heating at reflux, the reaction mixture was cooled to rt, diluted with water, and extracted with Et_2O. The combined organic extracts were cooled to 0 °C and acidified (pH <1) by addition of 35% hydrochloric acid. The organic layer was separated, discarded, and the aqueous layer was evaporated under reduced pressure. The residue was taken-up several times with absolute EtOH and evaporated under reduced pressure to remove residual water. The crude material was dried under reduced pressure to afford 3.85 g (93%) of 2-benzyloxybut-3-enylamine hydrochloride (**21**).

2-Benzyloxybut-3-enylamine (*free amine derived from hydrochloride* **21**): A sample of **21** was treated with a 15% aqueous NaOH solution. After extraction with Et_2O, the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 2-benzyloxybut-3-enylamine as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.30–7.18 (m, 5H), 5.61 (ddd, J=16.8, 11.0, 9.3 Hz, 1H), 5.09 (br d, J=11.0 Hz, 1H), 5.08 (br d, J=16.8 Hz, 1H), 4.44 (br s, 2H), 3.42 (dd, J=9.2, 5.7 Hz, 1H), 3.47 (dd, J=9.2, 6.9 Hz, 1H), 2.82 (dd, J=12.6, 4.8 Hz, 1H), 2.60 (dd, J=12.6, 7.7 Hz, 1H), 2.39–2.30 (m, 1H), 1.48 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 138.4 (s), 128.4 (d, 2C), 137.8 (d), 127.7 (2d, 3C), 117.3 (t), 73.1 (t), 71.8 (t), 47.5 (d), 43.4 (t).

To a solution of **21** (1.00 g, 4.39 mmol) in CH_2Cl_2 (40 mL) at 0 °C were successively added Et_3N (1.1 mL, 8.8 mL, 2 equiv), DMAP (54 mg, 0.44 mmol, 0.1 equiv), and TsCl (837 mg, 4.39 mmol, 1 equiv). After 1 h at rt, the reaction mixture was poured into a 1 M solution of hydrochloric acid and extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20 to 70:30) to provide 1.30 g (86%) of sulfonamide **22** as a colorless oil ($C_{19}H_{23}NO_3S$, MW=345.46 g mol^{-1}). IR 3281, 1641, 1598, 1495, 1454, 1420, 1325, 1157, 1091, 995, 920, 813, 736, 698, 660 cm^{-1}; ^{1}H NMR δ 7.73 (d, J=8.3 Hz, 2H), 7.40–7.27 (m, 7H), 5.60 (ddd, J=17.2, 10.5, 7.9 Hz, 1H), 5.13 (ddd, apparent dt, J=10.4, 1.0 Hz, 1H), 5.09 (ddd, apparent dt, J=17.4, 1.0 Hz, 1H), 5.01 (t, J=6.2 Hz, 1H, NH), 4.49 (d, AB syst, J=12.0 Hz, 1H), 4.45 (d, AB syst, J=12.0 Hz, 1H), 3.50 (dd, J=9.4, 4.8 Hz, 1H), 3.38 (dd, J=9.4, 7.6 Hz, 1H), 3.15–3.09 (m, 1H), 3.06–3.03 (m, 1H), 2.57–2.48 (m, 1H), 2.45 (s, 3H); ^{13}C NMR δ 143.2 (s), 137.7 (s), 136.9 (s), 135.5 (d), 129.6 (d, 2C), 128.4 (d, 2C), 127.7 (d), 127.5 (d, 2C), 127.0 (d, 2C), 118.0 (t), 73.1 (t), 71.9 (t), 45.2 (t), 43.0 (d), 21.4 (q); MS-EI m/z (relative intensity) 254 (M−Bn$^+$, 1), 237 (M−BnOH$^+$, 10), 190 (11), 184 (29), 155 (55), 108 (27), 107 (10), 92 (10), 91 (100), 82 (10), 65 (12), 54 (6).

4.3.4. (E)-4-(Dimethylphenylsilyl)but-3-en-1-ol (**24**)[19]

To a solution of (*E*)-alkenyl iodide **23**[18] (812 mg, 2.88 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (1.27 mL, 2.5 M in hexanes, 3.17 mmol, 1.1 equiv). After 45 min at −78 °C, chlorodimethylphenylsilane (580 μL, 3.45 mmol, 1.2 equiv) was added. After 1 h at 0 °C and 0.5 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and $TsOH\cdot H_2O$ (27 mg, 0.29 mmol, 0.05 equiv) was added. After 3 h at rt, the reaction mixture was neutralized by addition of a few drops of a saturated aqueous solution of $NaHCO_3$ and evaporated under reduced pressure. The residue was partitioned between H_2O and Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/toluene/Et_2O 50:30:20) to afford 414 mg (70%, two steps from **23**) of **24** as a colorless oil ($C_{12}H_{18}OSi$, MW=206.36 g mol^{-1}). IR 3322, 1617, 1427, 1247, 1114, 1045, 986, 818, 781, 728, 698 cm^{-1}; ^{1}H NMR δ 7.52–7.50 (m, 2H), 7.36–7.34 (m, 3H), 6.09 (dt, J=18.6, 6.3 Hz, 1H), 5.92 (dt, J=18.6, 1.4 Hz, 1H), 3.70 (t, J=6.3 Hz, 2H), 2.43 (apparent qd, J=6.3, 1.4 Hz, 2H), 1.40 (br s, 1H, OH), 0.34 (s, 6H); ^{13}C NMR δ 144.5 (d), 138.7 (s), 133.8 (d, 2C), 131.6 (d), 128.9 (d), 127.8 (d, 2C), 61.5 (t), 40.0 (t), −2.6 (q, 2C); MS-EI m/z (relative intensity) 191 (M−Me$^+$, 44), 178 (18), 164 (15), 163 (100), 151 (18), 145 (57), 137 (94), 130 (23), 121 (86), 119 (17), 105 (33), 104 (15), 91 (28), 78 (22), 75 (90), 61 (19), 59 (16), 53 (21).

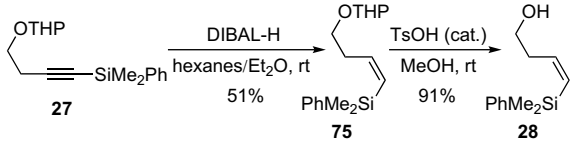
*4.3.5. 2-[(E)-4-(Dimethylphenylsilyl)but-3-enyl]-isoindole-1,3-dione (**25**)*

To a solution of **24** (405 mg, 1.96 mmol) in THF (10 mL) at 0 °C were successively added PPh_3 (618 mg, 2.35 mmol, 1.2 equiv), phthalimide (347 mg, 2.35 mmol, 1.2 equiv), and DIAD (467 μL, 2.35 mmol, 1.2 equiv). After 1 h at rt, the reaction mixture was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient 100:0 to 95:5) to afford 491 mg (74%) of **25** as a viscous oil ($C_{20}H_{21}NO_2Si$, MW=335.47 g mol^{-1}). IR 1772, 1707, 1616, 1392, 1356, 1247, 1112, 996, 818, 785, 717, 698 cm^{-1}; ^{1}H NMR δ 7.85–7.80 (m, 2H), 7.72–7.68 (m, 2H), 7.41–7.38 (m, 2H), 7.32–7.23 (m, 3H), 6.07 (dt, *J*=18.5, 6.6 Hz, 1H), 5.79 (br d, *J*=18.5 Hz, 1H), 3.80 (t, *J*=7.0 Hz, 2H), 2.52 (apparent br q, *J*=7.0 Hz, 2H), 0.24 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.2 (s, 2C), 144.2 (d), 138.5 (s), 133.8 (d, 2C), 133.7 (d, 2C), 132.0 (s, 2C), 131.6 (d), 128.8 (d), 127.6 (d, 2C), 123.1 (d, 2C), 37.0 (t), 35.4 (t), −2.8 (q, 2C); MS-EI *m*/*z* (relative intensity) 335 (M^+, 35), 320 ($M-Me^+$, 16), 261 (51), 204 (16), 185 (14), 184 (100), 182 (13), 160 (69), 145 (20), 135 (33), 130 (48), 121 (28), 105 (21), 77 (20).

*4.3.6. N-[(E)-4-(Dimethylphenylsilyl)but-3-enyl-4-methylbenzenesulfonamide (**26**)*

To a solution of **25** (468 mg, 1.39 mmol) in EtOH (5 mL) was added $N_2H_4\cdot H_2O$ (102 μL, 2.09 mmol, 1.3 equiv). After 2 h heating at reflux, the reaction mixture was diluted with H_2O and filtered (H_2O/EtOAc). The filtrate was evaporated under reduced pressure and the residue was partitioned between H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude primary amine was dissolved in pyridine (4 mL) and TsCl (320 mg, 1.67 mmol, 1.2 equiv) was added at 0 °C. After 48 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and diluted with EtOAc, the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 85:15) to provide 122 mg (24%, two steps from **25**) of sulfonamide **26** as a yellow oil ($C_{19}H_{25}NO_2SSi$, MW=359.56 g mol^{-1}). IR 3277, 1616, 1598, 1427, 1322, 1247, 1156, 1113, 1094, 988, 814, 784, 730, 699, 660 cm^{-1}; ^{1}H NMR δ 7.72 (d, *J*=8.3 Hz, 2H), 7.48–7.45 (m, 2H), 7.38–7.33 (m, 3H), 7.28 (d, *J*=8.3 Hz, 2H), 5.89 (dt, *J*=18.6, 6.1 Hz, 1H), 5.76 (dt, *J*=18.6, 1.2 Hz, 1H), 4.37 (t, *J*=6.0 Hz, 1H, NH), 3.04 (apparent q, *J*=6.6 Hz, 2H), 2.42 (s, 3H), 2.29 (apparent qd, *J*=6.6, 1.2 Hz, 2H), 0.30 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 143.6 (d), 143.4 (s), 138.4 (s), 136.9 (s), 133.7 (d, 2C), 132.1 (d), 129.7 (d, 2C), 129.0 (d), 127.8 (d, 2C), 127.1 (d, 2C), 41.8 (t), 36.3 (t), 21.5 (q), −2.6 (q, 2C); MS-EI *m*/*z* (relative intensity) 344 ($M-Me^+$, 14), 213 (15), 204 ($M-Ts^+$, 27), 185 (6), 184 (58), 155 (100), 145 (10), 135 (20), 121 (12), 91 (89), 78 (74), 77 (22), 65 (17), 52 (12), 51 (14).

*4.3.7. Preparation of homoallylic alcohol **28***



*4.3.7.1. Dimethylphenyl-[(Z)-4-(tetrahydropyran-2-yloxy)but-1-enyl]-silane (**75**).* To a solution of alkynylsilane **27**[20] (3.00 g, 10.4 mmol) in Et_2O (15 mL) at 0 °C was slowly added a solution of DIBAL-H (11.5 mL, 1 M in hexanes, 11.5 mmol, 1.1 equiv). After 20 h at rt, another quantity of DIBAL-H (10.5 mL, 10.5 mmol, 1.01 equiv) was added. After a further 2 h at rt, the reaction mixture was cautiously poured into a saturated aqueous solution of sodium potassium tartrate. The resulting mixture was diluted with EtOAc and stirred for 2 h. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O 97.5:2.5) to afford 1.55 g (51%) of **75** as a pale yellow oil ($C_{17}H_{26}O_2Si$, MW=290.47 g mol^{-1}). ^{1}H NMR ($CDCl_3$) δ 7.60–7.56 (m, 2H), 7.38–7.35 (m, 3H), 6.50 (dt, *J*=14.3, 7.3 Hz, 1H), 5.79 (br d, *J*=14.3 Hz, 1H), 4.55 (apparent t, *J*=3.4 Hz, 1H), 3.87–3.80 (m, 1H), 3.73 (dt, *J*=9.6, 7.0 Hz, 1H), 3.52–3.46 (m, 1H), 3.38 (dt, *J*=9.6, 6.8 Hz, 1H), 2.41 (apparent br q, *J*=7.0 Hz, 2H), 1.87–1.49 (m, 6H), 0.43 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 146.7 (d), 139.4 (s), 133.6 (d, 2C), 129.2 (d), 128.9 (d), 127.7 (d, 2C), 98.5 (d), 66.6 (t), 62.0 (t), 34.0 (t), 30.5 (t), 25.4 (t), 19.4 (t), −0.9 (q, 2C).

*4.3.7.2. (Z)-4-(Dimethylphenylsilyl)but-3-en-1-ol (**28**)*[19,20]. To a solution of **75** (1.48 g, 5.08 mmol) in MeOH (10 mL) was added $TsOH\cdot H_2O$ (10 mg, 0.052 mmol, 0.1 equiv). After 3 h at rt, the reaction mixture was neutralized by addition of a few drops of a saturated aqueous solution of $NaHCO_3$ and evaporated under reduced pressure. The residue was partitioned between H_2O and Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10) to afford 950 mg (91%, 46% for the two steps from alkynylsilane **27**) of **28** as a pale yellow oil ($C_{12}H_{18}OSi$, MW=206.36 g mol^{-1}). IR 3318, 1606, 1427, 1248, 1111, 1045, 816, 776, 729, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56–7.52 (m, 2H), 7.35–7.31 (m, 3H), 6.47 (dt, *J*=14.3, 7.0 Hz, 1H), 5.88 (dt, *J*=14.3, 1.2 Hz, 1H), 3.60 (t, *J*=6.6 Hz, 2H), 2.35 (apparent qd, *J*=6.6, 1.2 Hz, 2H), 1.66 (br s, 1H, OH), 0.45 (br s, 6H); ^{13}C NMR ($CDCl_3$) δ 146.0 (d), 139.3 (s), 133.6 (d, 2C), 130.3 (d), 128.9 (d), 127.8 (d, 2C), 61.9 (t), 36.8 (t), −0.96 (q, 2C); MS-EI *m*/*z* (relative intensity) 191 ($M-Me^+$, 26), 163 (40), 145 (54), 137 (69), 136 (14), 135 (100), 129 (43), 121 (37), 113 (83), 111 (34), 105 (27), 75 (64), 61 (16).

*4.3.8. 2-[(Z)-4-(Dimethylphenylsilyl)but-3-enyl]isoindole-1,3-dione (**29**)*

To a solution of alcohol **28** (956 mg, 4.63 mmol) in THF (5 mL) at 0 °C were successively added PPh_3 (1.21 g, 6.02 mmol, 1.3 equiv), phthalimide (681 mg, 6.02 mmol, 1.3 equiv), and DIAD (920 μL, 6.02 mmol, 1.3 equiv). After 3 h at rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O gradient 100:0 to 92:8) to give 1.38 g (88%) of **29** as a colorless oil ($C_{20}H_{21}NO_2Si$, MW=335.47 g mol^{-1}). IR 1772, 1707, 1608, 1393, 1358, 1248, 1108, 1020, 816, 779, 715, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82–7.78 (m, 2H), 7.71–7.66 (m, 2H), 7.49–7.46 (m, 2H), 7.29–7.23 (m, 3H), 6.43 (dt, *J*=14.4, 7.2 Hz, 1H), 5.79 (br d, *J*=14.0 Hz, 1H), 3.71 (t, *J*=7.0 Hz, 2H), 2.52 (apparent br q, *J*=7.2 Hz, 2H), 0.36 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.2 (s, 2C), 145.5 (d), 139.0 (s), 133.8 (d, 2C), 133.5 (d, 2C), 132.0 (s, 2C), 130.3 (d), 128.8 (d), 127.7 (d, 2C), 123.1 (d, 2C), 37.3 (t), 32.7 (t), −1.0 (q, 2C); MS-EI *m*/*z* (relative intensity) 335 (M^+, 36), 320 (16), 261 (49), 204 (15), 185 (14), 184 (100), 182 (15), 160 (58), 145 (160), 135 (29), 130 (40), 121 (16), 105 (16), 77 (13).

*4.3.9. N-[(Z)-4-(Dimethylphenylsilyl)but-3-enyl]-4-methylbenzenesulfonamide (**30**)*

To a solution of phthalimide **29** (650 mg, 1.94 mmol) in EtOH (5 mL) was added hydrazine monohydrate (0.12 mL, 2.5 mmol,

1.3 equiv). After 2 h heating at reflux, the reaction mixture was diluted with H_2O and filtered (H_2O/EtOAc). The filtrate was evaporated under reduced pressure and the residue was partitioned between H_2O and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude primary amine was dissolved in pyridine (5 mL) and TsCl (445 mg, 2.32 mmol, 1.2 equiv) was added at 0 °C. After 16 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient 95:5 to 85:15) to afford 516 mg (74%, two steps from **29**) of **30** as a yellow oil ($C_{19}H_{25}NO_2SSi$, MW=359.56 g mol^{-1}). IR 3277, 1600, 1427, 1323, 1248, 1156, 1110, 1093, 814, 778, 731, 700, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J=8.1 Hz, 2H), 7.54–7.50 (m, 2H), 7.38–7.34 (m, 3H), 7.29 (d, J=8.1 Hz, 2H), 6.22 (dt, J=14.3, 7.0 Hz, 1H), 5.80 (br d, J=14.3 Hz, 1H), 4.16 (t, J=6.0 Hz, 1H, NH), 2.88 (apparent br q, J=6.6 Hz, 2H), 2.44 (s, 3H), 2.29 (apparent qd, J=7.0, 1.2 Hz, 2H), 0.37 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.2 (d), 143.3 (s), 139.1 (s), 136.8 (s), 133.6 (d, 2C), 131.2 (d), 129.6 (d, 2C), 129.1 (d), 127.9 (d, 2C), 127.1 (d, 2C), 42.4 (t), 33.2 (t), 21.5 (q), −1.1 (q, 2C); MS-EI m/z (relative intensity) 344 (M−Me$^+$, 20), 282 (10), 266 (7), 213 (15), 204 (29), 184 (67), 156 (10), 155 (100), 149 (10), 145 (11), 135 (28), 121 (10), 105 (9), 91 (68), 78 (17), 65 (12).

4.3.10. *tert*-Butyl (*E*)-5-phenyl-5-(toluene-4-sulfonylamino)-pent-2-enoate (**31**)

To a solution of sulfonamide **15** (380 mg, 1.26 mmol) in CH_2Cl_2 (30 mL) were added *tert*-butyl acrylate (554 μL, 3.78 mmol, 3 equiv) and Grubbs II catalyst (53 mg, 0.063 mmol, 0.05 equiv). After 12 h at rt and 5 h heating at reflux, another quantity of Grubbs II catalyst (26 mg, 0.031 mmol, 0.025 equiv) was added. After 3 h at reflux, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10, 85:15) to afford 425 mg (84%) of **31** as a pale brown solid ($C_{22}H_{27}NO_4S$, MW=401.52 g mol^{-1}). Mp 125 °C; IR 3268, 1706, 1687, 1654, 1322, 1147, 1092, 1070, 984, 808, 699, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J=8.2 Hz, 2H), 7.17–7.12 (m, 5H), 7.05–7.02 (m, 2H), 6.53 (dt, J=15.5, 7.3 Hz, 1H), 5.70 (d, J=15.5 Hz, 1H), 5.21 (d, J=7.2 Hz, 1H, NH), 4.41 (apparent q, J=7.0 Hz, 1H), 2.67–2.51 (m, 2H), 2.35 (s, 3H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.2 (s), 143.2 (s), 141.5 (d), 139.6 (s), 137.3 (s), 129.4 (d, 2C), 128.6 (d, 2C), 127.7 (d), 127.1 (d, 2C), 126.6 (d), 126.5 (d, 2C), 80.4 (s), 57.0 (d), 39.8 (t), 28.1 (q, 3C), 21.5 (q); MS-EI m/z (relative intensity) 328 (M−t-BuO$^+$, 2), 262 (6), 261 (16), 260 (100), 155 (37), 104 (5), 91 (47), 65 (6), 57 (6), 56 (22), 55 (8).

4.3.11. *N*-[(*E*)-5-Hydroxy-1-phenylpent-3-enyl]-4-methylbenzenesulfonamide (**32**)

To a solution of **31** (250 mg, 0.623 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise a solution of DIBAL-H (1.9 mL, 1 M in hexanes, 1.9 mmol, 3 equiv). After 15 min at −78 °C, the reaction mixture was warmed to rt over 1.5 h and then cautiously poured into a saturated aqueous solution of sodium potassium tartrate. After 1 h stirring, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 60:40) to give 130 mg (64%) of **32** as a colorless oil ($C_{18}H_{21}NO_3S$, MW=331.43 g mol^{-1}). IR 3482, 3272, 1598, 1495, 1455, 1319, 1304, 1289, 1152, 1091, 1055, 970, 812, 758, 699, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J=8.2 Hz, 2H), 7.14–7.02 (m, 7H), 5.83 (d, J=7.5 Hz, 1H, NH), 5.65 (dt, J=15.4, 5.6 Hz, 1H), 5.42 (dt, J=15.4, 7.0 Hz, 1H), 4.38 (apparent q, J=7.0 Hz, 1H), 3.98 (d, J=5.6 Hz, 2H), 2.47–2.31 (m, 3H, 2H+OH), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.1 (s), 140.6 (s), 137.6 (s), 133.8 (d), 129.3 (d, 2C), 128.3 (d, 2C), 127.2 (d), 127.1 (d, 2C), 126.6 (d), 126.5 (d, 2C), 63.1 (t), 57.5 (d), 40.3 (t), 21.5 (q).

4.3.12. *N*-[(*E*)-5-(tert-Butyldimethylsilyloxy)-1-phenylpent-3-enyl]-4-methylbenzenesulfonamide (**33**)

To a solution of alcohol **32** (122 mg, 0.368 mmol) and imidazole (58 mg, 0.85 mmol, 2.3 equiv) in DMF (5 mL) was added *tert*-butylchlorodimethylsilane (91 mg, 0.60 mmol, 1.6 equiv). After 3 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl, diluted with H_2O, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10) to afford 164 mg (99%) of **33** as a white solid ($C_{24}H_{35}NO_3SSi$, MW=445.69 g mol^{-1}). Mp 81 °C; IR 3251, 1600, 1458, 1322, 1251, 1159, 1096, 1054, 965, 834, 813, 776, 705, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J=8.3 Hz, 2H), 7.19–7.13 (m, 5H), 7.08–7.04 (m, 2H), 5.57 (dt, J=15.4, 4.8 Hz, 1H), 5.33 (dt, J=15.4, 7.0 Hz, 1H), 4.84 (d, J=6.4 Hz, 1H, NH), 4.35 (apparent q, J=6.6 Hz, 1H), 4.08 (dd, J=4.8, 1.1 Hz, 2H), 2.50–2.39 (m, 2H), 2.37 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.1 (s), 140.3 (s), 137.5 (s), 134.2 (d), 129.3 (d, 2C), 128.4 (d, 2C), 127.4 (d), 127.1 (d, 2C), 126.6 (d, 2C), 124.6 (d), 63.3 (t), 57.2 (d), 40.3 (t), 25.9 (q, 3C), 21.5 (q), 18.4 (s), −5.2 (q, 2C); MS-EI m/z (relative intensity) 430 (M−Me$^+$, 1), 388 (M−t-Bu$^+$, 24), 261 (17), 260 (100), 228 (33), 155 (37), 144 (8), 143 (66), 128 (9), 113 (10), 91 (57), 75 (23), 73 (15).

4.4. Preparation of trimethylsilyl-1,6-ene-ynamides of type H from sulfonamides of type I

4.4.1. 4-Methyl-*N*-(1-phenylbut-3-enyl)-*N*-(trimethylsilylethynyl)benzenesulfonamide (**35**) (representative procedure)

To a solution of sulfonamide **15** (1.00 g, 3.32 mmol) in toluene (40 mL) at 0 °C was added a solution of KHMDS (7.3 mL, 0.5 M in toluene, 3.65 mmol, 1.1 equiv). After 1 h at 0 °C, (trimethylsilylethynyl)phenyliodonium triflate (**34**) (1.79 g, 3.98 mmol, 1.2 equiv) was added portionwise. After 24 h at rt, the reaction mixture was filtered through Celite (toluene/Et_2O 80:20). The filtrate was evaporated under reduced pressure and the crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10) to afford 790 mg (60%) of ynamide **35** as a yellow oil ($C_{22}H_{27}NO_2SSi$, MW=397.61 g mol^{-1}). IR 2156, 1643, 1597, 1494, 1366, 1248, 1167, 1089, 972, 919, 838, 812, 758, 739, 698, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J=8.4 Hz, 2H), 7.26–7.11 (m, 7H), 5.60 (ddt, J=17.0, 9.9, 7.0 Hz, 1H), 5.09 (apparent dq, J=17.0, 1.5 Hz, 1H), 4.97 (m, 1H), 4.92 (dd, J=9.2, 6.2 Hz, 1H), 2.77 (m, 1H), 2.56 (m, 1H), 2.37 (s, 3H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.1 (s), 138.8 (s), 135.2 (s), 133.5 (d), 129.1 (d, 2C), 128.3 (d, 2C), 128.1 (d), 127.9 (d, 2C), 127.2 (d, 2C), 118.3 (t), 93.2 (s), 86.3 (s), 62.9 (d), 38.2 (t), 21.6 (q), 0.1 (q, 3C); MS-EI m/z (relative intensity) 397 (M$^+$, 1), 356 (M−Allyl$^+$, 13), 242 (M−Ts$^+$, 31), 155 (53), 132 (12), 131 (100), 130 (19), 129 (15), 91 (60), 73 (14).

4.4.2. *N*-[2-(Benzyloxymethyl)but-3-enyl]-4-methyl-*N*-(trimethylsilylethynyl)benzenesulfonamide (**36**)

This compound was synthesized from sulfonamide **22** (638 mg, 1.85 mmol) in toluene (22 mL) with KHMDS (4.8 mL, 0.5 M in toluene, 2.4 mmol, 1.3 equiv) and iodonium triflate **34** (1.17 g, 2.58 mmol, 1.4 equiv) according to the representative procedure (14 h at rt). After purification by flash chromatography on silica gel (petroleum ether/Et_2O 95:5 then petroleum ether/EtOAc 95:5), 515 mg (63%) of ynamide **36** was obtained as a colorless oil

($C_{24}H_{31}NO_3SSi$, MW=441.66 g mol^{-1}). IR 2160, 1597, 1495, 1454, 1366, 1248, 1169, 1090, 1000, 920, 840, 813, 735, 697, 659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J=8.3 Hz, 2H), 7.34–7.20 (m, 7H), 5.72 (ddd, J=17.3, 10.4, 8.1 Hz, 1H), 5.13 (dt, J=17.3, 1.3 Hz, 1H), 5.09 (dt, J=10.4, 1.3 Hz, 1H), 4.49 (d, AB syst, J=12.0 Hz, 1H), 4.45 (d, AB syst, J=12.0 Hz, 1H), 3.52–3.46 (m, 2H), 3.46 (dd, J=12.9, 6.9 Hz, 1H), 3.31 (dd, J=12.9, 7.8 Hz, 1H), 2.83–2.74 (m, 1H), 2.43 (s, 3H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.5 (s), 138.1 (s), 135.8 (d), 134.3 (s), 129.5 (d, 2C), 128.2 (d, 2C), 127.7 (2d, 3C), 127.4 (d, 2C), 117.9 (t), 95.3 (s), 73.2 (s), 73.0 (t), 70.5 (t), 52.5 (t), 42.7 (d), 21.5 (q), 0.0 (q, 3C); MS-EI m/z (relative intensity) 441 (M^+, 1), 426 ($M-Me^+$, 2), 286 (13), 203 (6), 180 (3), 155 (10), 131 (16), 110 (7), 92 (9), 91 (100), 73 (22), 65 (6).

4.4.3. *N-[(E)-4-(Dimethylphenylsilyl)but-3-enyl]-4-methyl-N-(trimethylsilylethynyl)benzenesulfonamide (**37**)*

This compound was synthesized from sulfonamide **26** (65 mg, 0.18 mmol) in toluene (5 mL) with KHMDS (0.55 mL, 0.5 M in toluene, 0.28 mmol, 1.5 equiv) and iodonium triflate **34** (135 mg, 0.299 mmol, 1.7 equiv) according to the representative procedure (14 h at rt). After purification by chromatography on silica gel (petroleum ether/Et_2O 97.5:2.5), 40 mg (48%) of ynamide **37** was obtained as a yellow oil ($C_{24}H_{33}NO_2SSi_2$, MW=455.76 g mol^{-1}). IR 2161, 1617, 1597, 1427, 1369, 1248, 1169, 1113, 1091, 985, 838, 729, 698, 659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J=8.3 Hz, 2H), 7.51–7.48 (m, 2H), 7.37–7.30 (m, 5H), 6.0 (dt, J=18.6, 6.1 Hz, 1H), 5.84 (dt, J=18.6, 1.3 Hz, 1H), 3.93 (t, J=7.5 Hz, 2H), 2.50–2.42 (m, 2H), 2.44 (s, 3H), 0.31 (s, 6H), −0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.5 (s), 143.2 (d), 138.6 (s), 134.5 (s), 133.8 (d, 2C), 131.5 (d), 129.6 (d, 2C), 128.9 (d), 127.7 (2d, 2C+2C), 94.9 (s), 73.4 (s), 50.3 (t), 34.9 (t), 21.6 (q), 0.1 (q, 3C), −2.7 (q, 2C); MS-EI m/z (relative intensity) 455 (M^+, 1), 440 ($M-Me^+$, 4), 309 (19), 307 (12), 301 (24), 300 ($M-Ts^+$, 80), 280 (16), 216 (12), 155 (22), 150 (11), 149 (31), 136 (14), 135 (100), 121 (20), 110 (13), 91 (43), 73 (36), 59 (14).

4.4.4. *N-[(Z)-4-(Dimethylphenylsilyl)but-3-enyl]-4-methyl-N-(trimethylsilylethynylbenzene)sulfonamide (**38**)*

This compound was synthesized from sulfonamide **30** (407 mg, 1.13 mmol) in toluene (15 mL) with KHMDS (3.2 mL, 0.5 M in toluene, 1.6 mmol, 1.4 equiv) and iodonium triflate **34** (765 mg, 1.70 mmol, 1.5 equiv) according to the representative procedure (14 h at rt). After purification by chromatography on silica gel (petroleum ether/Et_2O 97.5:2.5), 445 mg (86%) of ynamide **38** was obtained as a pale yellow oil ($C_{24}H_{33}NO_2SSi_2$, MW=455.76 g mol^{-1}). IR 2160, 1599, 1369, 1248, 1169, 1111, 1091, 997, 837, 814, 778, 756, 730, 699, 659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J=8.3 Hz, 2H), 7.52–7.49 (m, 2H), 7.35–7.29 (m, 5H), 6.32 (dt, J=14.0, 7.4 Hz, 1H), 5.77 (dt, J=14.0, 0.9 Hz, 1H), 3.26 (br t, J=7.4 Hz, 2H), 2.44 (s, 3H), 2.39 (apparent qd, J=7.4, 0.9 Hz, 2H), 0.36 (s, 6H), −0.14 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.5 (s+d, 2C), 139.0 (s), 134.5 (s), 133.6 (d, 2C), 130.8 (d), 129.6 (d, 2C), 129.0 (d), 127.9 (d, 2C), 127.8 (d, 2C), 94.9 (s), 73.4 (s), 50.7 (t), 32.0 (t), 21.6 (q), 0.0 (q, 3C), −1.0 (q, 2C); MS-EI m/z (relative intensity) 440 ($M-Me^+$, 2), 309 (19), 307 (11), 302 (8), 301 (23), 300 ($M-Ts^+$, 77), 270 (11), 155 (21), 149 (17), 136 (14), 135 (100), 121 (14), 110 (12), 91 (45), 75 (12), 73 (41), 59 (14); HRMS calcd for $C_{24}H_{34}NO_2SSi_2$ ($M+H^+$): 456.1849, found: 456.1856.

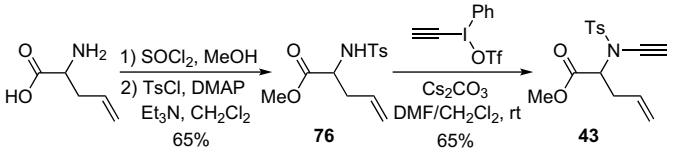
4.4.5. *N-[(E)-5-(tert-Butyldimethylsilyloxy)-1-phenylpent-3-enyl]-4-methyl-N-(trimethylsilylethynyl)benzenesulfonamide (**39**)*

This compound was synthesized from sulfonamide **33** (172 mg, 0.386 mmol) in toluene (5 mL) with KHMDS (1.1 mL, 0.5 M in toluene, 0.55 mmol, 1.4 equiv) and iodonium triflate **34** (261 mg, 0.578 mmol, 1.5 equiv) according to the representative procedure (15 h at rt). After purification by chromatography on silica gel (petroleum ether/Et_2O 90:10), 105 mg (50%) of ynamide **39** was obtained as a yellow solid ($C_{29}H_{43}NO_3SSi_2$, MW=541.89 g mol^{-1}). Mp 65 °C; IR 2160, 1598, 1458, 1371, 1250, 1169, 1122, 1091, 1054, 967, 839, 813, 776, 699, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J=8.3 Hz, 2H), 7.27–7.17 (m, 5H), 7.13 (d, J=8.3 Hz, 2H), 5.62 (dt, J=15.4, 5.1 Hz, 1H), 5.42 (dt, J=15.4, 7.0 Hz, 1H), 4.89 (dd, J=9.0, 6.7 Hz, 1H), 3.99 (dd, J=5.1, 0.8 Hz, 2H), 2.79–2.71 (m, 1H), 2.60–2.53 (m, 1H), 2.38 (s, 3H), 0.89 (s, 9H), 0.18 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.0 (s), 138.8 (s), 135.1 (s), 133.1 (d), 129.0 (d, 2C), 128.2 (d, 2C), 128.0 (d), 127.7 (d, 2C), 127.1 (d, 2C), 125.6 (d), 93.2 (s), 76.4 (s), 63.6 (t), 63.0 (d), 36.8 (t), 25.9 (q, 3C), 21.5 (q), 18.4 (s), 0.1 (q, 3C), −5.2 (q, 2C). Anal. Calcd for $C_{29}H_{43}NO_3SSi_2$: C, 64.28; H, 8.00; N, 2.58. Found: C, 64.27; H, 8.15; N, 2.51.

4.4.6. *4-Methyl-N-(3-methyl-1-phenylbut-3-enyl)-N-(trimethylsilylethynyl)benzenesulfonamide (**40**)*

This compound was synthesized from sulfonamide **16** (382 mg, 1.21 mmol) in toluene (22 mL) with KHMDS (3.64 mL, 0.5 M in toluene, 1.82 mmol, 1.5 equiv) and iodonium triflate **34** (870 mg, 1.94 mmol, 1.6 equiv) according to the representative procedure (48 h at rt). After purification by chromatography on silica gel (petroleum ether/Et_2O 95:5), 336 mg (67%) of **40** was obtained as a pale yellow oil ($C_{23}H_{29}NO_2SSi$, MW=411.63 g mol^{-1}). IR 2158, 1650, 1597, 1365, 1248, 1166, 1090, 962, 839, 812, 758, 738, 698, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J=8.2 Hz, 2H), 7.28–7.14 (m, 5H), 7.10 (d, J=8.2 Hz, 2H), 5.09 (dd, J=9.3, 6.1 Hz, 1H), 4.76 (br s, 1H), 4.74 (br s, 1H), 2.78 (dd, J=14.4, 9.3 Hz, 1H), 2.45 (dd, J=14.4, 6.1 Hz, 1H), 2.36 (s, 3H), 1.72 (s, 3H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.0 (s), 140.3 (s), 139.0 (s), 135.1 (s), 128.9 (d, 2C), 128.2 (d, 2C), 127.9 (d), 127.8 (d, 2C), 127.1 (d, 2C), 114.5 (t), 93.2 (s), 77.2 (s), 61.2 (d), 42.1 (t), 22.1 (q), 21.5 (q), 0.0 (q, 3C); MS-EI m/z (relative intensity) 411 (M^+, 3), 396 ($M-Me^+$, 3), 356 (8), 256 (22), 240 (6), 186 (10), 155 (36), 146 (12), 145 (100), 144 (28), 143 (14), 130 (14), 129 (67), 128 (40), 127 (12), 117 (17), 115 (13), 91 (56), 73 (23), 65 (9); HRMS calcd for $C_{23}H_{30}NO_2SSi$ ($M+H^+$): 412.1767, found: 412.1764.

4.5. Preparation of the terminal 1,6-ene-ynamide 43[27]



4.5.1. *Methyl 2-(toluene-4-sulfonylamino)pent-4-enoate (**76**)*

To a solution of allylglycine (2.02 g, 17.5 mmol) in MeOH (35 mL) at 0 °C was added dropwise thionyl chloride (1.53 mL, 20.9 mmol, 1.2 equiv). After 12 h at rt, the reaction mixture was concentrated under reduced pressure. The residue was crystallized in Et_2O/EtOAc (95:5) and allylglycine methyl ester hydrochloride was dissolved in CH_2Cl_2 (70 mL). To the resulting solution at 0 °C were successively added Et_3N (7.3 mL, 53 mmol, 3 equiv), DMAP (214 mg, 1.75 mmol, 0.1 equiv), and TsCl (4.02 g, 21.05 mmol, 1.2 equiv). After 24 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient 90:10 to 75:25) to afford 3.33 g (65%) of sulfonamide **76** as a viscous yellow oil ($C_{13}H_{17}NO_4S$, MW=283.34 g mol^{-1}). IR 3268, 1748, 1597, 1432, 1339, 1160, 1092, 922, 814, 750, 662 cm^{-1}; ^{1}H NMR δ 7.71 (d, J=8.5 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 5.61 (ddt, J=17.6, 10.0, 7.0 Hz, 1H), 5.18 (d, J=9.0 Hz, 1H, NH), 5.12–5.04 (m, 2H), 4.02 (dt, J=9.0, 6.0 Hz, 1H), 3.51 (s, 3H), 2.45 (dd, apparent t, J=6.5 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR δ 171.3 (s), 143.7 (s), 136.8 (s), 131.2 (d), 129.6 (d, 2C), 127.2 (d, 2C), 119.7 (t), 55.2 (d), 52.4 (q), 37.5 (t), 21.5 (q); MS-EI m/z

(relative intensity) 283 (M^+, 1), 243 (8), 242 (M−Allyl$^+$, 63), 224 (M−CO_2Me^+, 22), 156 (9), 155 (100), 92 (9), 91 (91), 65 (15).

4.5.2. Methyl 2-[ethynyl(toluene-4-sulfonyl)amino]pent-4-enoate (**43**)[27]

To a solution of sulfonamide **76** (567 mg, 2.00 mmol) in DMF (15 mL) was added Cs_2CO_3 (850 mg, 2.60 mmol, 1.3 equiv). After 1 h at rt, a stirred suspension of ethynylphenyliodonium triflate (1.0 g, 2.6 mmol, 1.3 equiv) in CH_2Cl_2 (10 mL+5 mL rinse) was added via a cannula. After 2 h at rt, the reaction mixture was diluted with H_2O (60 mL). The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 75:25) to afford 500 mg (65%) of **43** as a colorless oil ($C_{15}H_{17}NO_4S$, MW=307.36 g mol^{-1}). IR 3283, 2133, 1744, 1644, 1596, 1436, 1366, 1258, 1164, 1089, 1012, 924, 813, 704, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.4 Hz, 2H), 5.64 (ddt, J=17.0, 10.1, 6.8 Hz, 1H), 5.16 (apparent dq, J=17.0, 1.3 Hz, 1H), 5.05 (apparent dq, J=10.1, 1.3 Hz, 1H), 4.53 (dd, apparent t, J=10.0, 5.1 Hz, 1H), 3.56 (s, 3H), 2.85 (s, 1H), 2.73–2.65 (m, 1H), 2.62–2.55 (m, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 144.9 (s), 134.7 (s), 131.9 (d), 129.5 (d, 2C), 128.0 (d, 2C), 119.3 (t), 72.8 (s), 61.7 (d), 60.4 (d), 52.4 (q), 33.9 (t), 21.6 (q); MS-EI m/z (relative intensity) 307 (M^+, 1), 306 (3), 292 (M−Me$^+$, 2), 248 (M−CO_2Me^+, 19), 200 (25), 184 (30), 155 (26), 139 (28), 120 (9), 110 (14), 92 (33), 91 (100), 81 (8), 71 (17), 67 (7), 65 (24), 59 (13), 52 (12). Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.57; N, 4.56. Found: C, 58.79; H, 5.35; N, 4.56.

4.6. Diastereoselective gold-catalyzed cycloisomerizations of 1,6-ene-ynamides

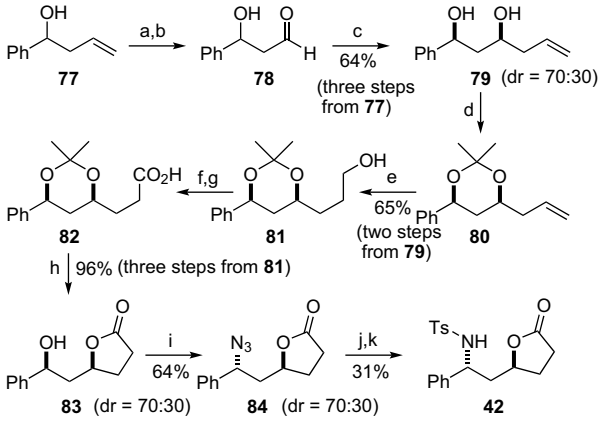
4.6.1. 4-Methyl-N-[(R*)-2-((2S*)-2-oxocyclobutyl)-1-phenylethyl]benzenesulfonamide (**41**) (representative procedure)

To a solution of ynamide **35** (115 mg, 0.289 mmol) in CH_2Cl_2 (5 mL) was added AuCl (3.4 mg, 0.012 mmol, 0.05 equiv). After 24 h at rt, the reaction mixture was filtered through a short plug of Celite (CH_2Cl_2) and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) to afford 77 mg (77%) of cyclobutanone **41** as a colorless oil (88:12 inseparable mixture of diastereomers) ($C_{19}H_{21}NO_3S$, MW=343.44 g mol^{-1}). IR 3271, 1771, 1599, 1495, 1456, 1324, 1155, 1089, 813, 701, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (br d, J=8.1 Hz, 2H), 7.16–7.14 (m, 3H), 7.11 (d, J=8.1 Hz, 2H), 7.05–7.01 (m, 2H), 6.04 (br d, J=8.5 Hz, 1H, NH), 4.53 (ddd, apparent dt, J=8.5, 6.0 Hz, 1H), 3.14–3.05 (m, 1H), 2.99 (dddd, J=18.1, 11.0, 8.5, 2.5 Hz, 1H), 2.85 (dddd, J=18.1, 9.5, 4.5, 2.5 Hz, 1H), 2.34 (s, 3H), 2.09 (m, 1H), 2.00–1.90 (m, 2H), 1.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 212.0 (s), 142.9 (s), 139.8 (s), 137.9 (s), 129.3 (d, 2C), 128.5 (d, 2C), 127.4 (d), 127.0 (d, 2C), 126.3 (d, 2C), 56.2 (d), 55.9 (d), 44.1 (t), 36.8 (t), 21.4 (q), 14.2 (t); MS-EI m/z (relative intensity) 343 (M^+, 1), 315 (4), 261 (17), 260 (100), 188 (M−Ts$^+$, 15), 155 (58), 130 (10), 106 (11), 104 (12), 91 (84), 77 (9), 65 (12), 55 (8).

4.6.2. 4-Methyl-N-[(R*)-2-((2S*)-5-oxotetrahydrofuran-2-yl)-1-phenylethyl]benzenesulfonamide (**42**) (representative procedure for gold-catalyzed cycloisomerization and Baeyer–Villiger oxidation)

To a solution of ynamide **35** (379 mg, 0.953 mmol) in CH_2Cl_2 (5 mL) was added AuCl (22 mg, 0.095 mmol, 0.1 equiv). After 24 h at rt, the reaction mixture was filtered through Celite (CH_2Cl_2) and the filtrate was evaporated under reduced pressure. The crude cyclobutanone **41** was dissolved in AcOH (5 mL) and $AcONa\cdot 3H_2O$ (154 mg, 1.14 mmol, 1.2 equiv) and AcOOH (0.74 mL, 35% solution in AcOH, 3.8 mmol, 4 equiv) were successively added. After 3 h at rt, the reaction mixture was cooled in an ice-bath and hydrolyzed with a 25% aqueous solution of $Na_2S_2O_3$. After addition of H_2O and extraction with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc 60:40, 50:50) to afford 110 mg (65%) of lactone **42** as a pale yellow solid ($C_{19}H_{21}NO_4S$, MW=359.44 g mol^{-1}). Mp 164 °C; IR 3201, 1755, 1324, 1183, 1150, 1093, 1059, 923, 843, 815, 765, 706, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (br d, J=8.0 Hz, 2H), 7.17–7.14 (m, 3H), 7.11 (d, J=8.0 Hz, 2H), 7.03–6.99 (m, 2H), 5.59 (d, J=8.6 Hz, 1H, NH), 4.60 (ddd, apparent td, J=8.6, 4.6 Hz, 1H), 4.52–4.45 (m, 1H), 2.47–2.42 (m, 2H), 2.34 (s, 3H), 2.30–2.22 (m, 1H), 2.09–1.96 (m, 2H), 1.83–1.73 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.5 (s), 143.3 (s), 139.9 (s), 137.4 (s), 129.4 (d, 2C), 128.7 (d, 2C), 127.6 (d), 127.1 (d, 2C), 126.2 (d, 2C), 77.2 (d), 55.2 (d), 43.1 (t), 28.7 (t), 28.0 (t), 21.4 (q); MS-EI m/z (relative intensity) 281 (M−PhH$^+$, 3), 261 (16), 260 (100), 207 (8), 155 (36), 104 (9), 91 (40). Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.11; H, 5.84; N, 3.74.

4.6.3. Chemical correlation for the attribution of the relative configuration of γ-lactone **42** and cyclobutanone **41**



Reagents and conditions: (a) OsO_4 (1 mol%), NMO, acetone/H_2O (4:1); (b) $NaIO_4$, THF/H_2O (1:1); (c) $AllylSnCl_3$, CH_2Cl_2, −78 °C to rt; (d) 2,2-dimethoxypropane, CSA (cat.), acetone, rt; (e) $BH_3\cdot$THF, THF, 0 °C then NaOH, H_2O_2; (f) IBX, THF/DMSO (1:1), rt; (f) $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4, t-BuOH/H_2O (7:2); (h) 80% aq AcOH then CSA (cat.), toluene, reflux; (i) $(PhO)_2P(O)N_3$, DBU, toluene, rt; (j) PPh_3, THF/H_2O (9:1), 50 °C; (k) TsCl, Py. CSA=10-camphor-sulfonic acid, IBX=2-iodoxybenzoic acid, DBU=1,8-diaza-bicyclo[5.4.0]undec-7-ene.

An authentic sample of lactone **42** was synthesized by an independent route. Homoallylic alcohol **77** was dihydroxylated [OsO_4 (1 mol%), NMO (1.1 equiv), acetone/H_2O (4:1), rt, 18 h] and the resulting triol (91%) underwent oxidative cleavage [$NaIO_4$, THF/H_2O (1:1), rt] to afford the β-hydroxyaldehyde **78**. The latter crude compound was allylated with allyltrichlorostannane (generated from allyltrimethylsilane and $SnCl_4$, CH_2Cl_2, rt) to obtain the 1,3-diol **79** (64%, three steps from **77**, *syn*/*anti*=70:30).[39] After formation of the acetonide **80**, which confirmed the *syn* relative configuration of the major diastereomer,[40] the terminal alkene underwent hydroboration followed by alkaline oxidative work-up to afford the primary alcohol **81** (65%). Oxidation of alcohol **35** gave the corresponding aldehyde [IBX, THF/DMSO (1:1), rt], which was oxidized to the carboxylic acid **82** [$NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4, t-BuOH/H_2O (7:2), rt]. The carboxylic acid **82** underwent acetonide hydrolysis (80% aq AcOH) and, after removal of water and AcOH by azeotropic evaporation with toluene, lactonization [CSA (cat.), toluene, reflux] afforded γ-lactone **83** (96%, three steps from **81**). Conversion of the benzylic alcohol in compound **83** to the

corresponding azide, with inversion of configuration (DPPA, DBU, toluene, rt),[41] provided compound **84** (64%, dr=70:30). After reduction [PPh_3, THF/H_2O (9:1), rt] and tosylation of the resulting primary amine (TsCl, Py, rt), a 70:30 mixture of diastereomers was formed and the major one was found to be identical to lactone **42** (31% isolated yield, two steps from **84**).

*4.6.3.1. 1-Phenylhex-5-en-1,3-diol (**79**).* To a solution of alcohol **77** (3.58 g, 24.2 mmol) in acetone/H_2O (4:1, 50 mL) were added NMO (3.06 g, 26.1 mmol, 1.1 equiv) and OsO_4 (1.5 mL, 4% in H_2O, 0.245 mmol, 0.01 equiv). After 18 h at rt, Celite (5 g) and finely ground $Na_2S_2O_3\cdot 5H_2O$ (4 g) were added to the reaction mixture. After 1 h, the resulting mixture was filtered through Celite (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was adsorbed on silica gel and purified by flash chromatography on silica gel (petroleum ether/EtOAc 70:30, 0:100 then EtOAc/EtOH 90:10) to afford 4.03 g (91%) of the corresponding triol as a waxy solid.[42] To a solution of the latter triol (2.0 g, 11 mmol) in THF/H_2O (1:1, 80 mL) was added $NaIO_4$ (9.4 g, 44 mmol, 4 equiv). After 1 h at rt, the reaction mixture was diluted with a saturated aqueous solution of NH_4Cl and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude β-hydroxyaldehyde **78** was dissolved in CH_2Cl_2 (25 mL) and a solution of allyltrichlorostannane [36 mL, 0.365 M stock solution in CH_2Cl_2 (prepared from $allylSiMe_3$ (3.18 mL, 20 mmol) and $SnCl_4$ (2.35 mL, 20 mmol) in CH_2Cl_2 (50 mL), rt, 14 h), 13.2 mmol, 1.2 equiv] was added at −78 °C. After 1 h at −78 °C, the reaction mixture was allowed to warm to rt and then successively treated with MeOH (5 mL) and a saturated aqueous solution of NH_4Cl (10 mL). The resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc gradient 85:15 to 75:25) to afford 1.50 g (71%, 64% three steps from **77**) of the 1,3-diol **79**[43] as an oil and as a 70:30 inseparable mixture of *syn*/*anti* diastereomers ($C_{12}H_{16}O_2$, MW=192.25 g mol^{-1}). Major (1*S**,3*S**) *syn*-diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.36–7.24 (m, 5H), 5.85–5.71 (m, 1H), 5.15–5.08 (m, 2H), 4.91 (dd, *J*=9.0, 3.8 Hz, 1H), 4.00–3.88 (m, 1H), 3.63 (br s, 1H, OH), 3.22 (br s, 1H, OH), 2.29–2.20 (m, 2H), 1.94–1.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 144.3 (s), 134.1 (d), 128.4 (d, 2C), 127.5 (d), 125.6 (d, 2C), 118.3 (t), 75.1 (d), 71.5 (d), 44.8 (t), 42.4 (t). Minor (1*S**,3*R**) *anti*-diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.35–7.24 (m, 5H), 5.85–5.71 (m, 1H), 5.14–5.08 (m, 2H), 5.03 (apparent br d, *J*=7.0 Hz, 1H), 4.00–3.88 (m, 1H), 3.27 (br s, 1H, OH), 2.60 (br s, 1H, OH), 2.29–2.20 (m, 2H), 1.94–1.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 144.4 (s), 134.4 (d), 128.4 (d, 2C), 127.2 (d), 125.5 (d, 2C), 118.3 (t), 71.5 (d), 67.9 (d), 44.0 (t), 41.9 (t).

*4.6.3.2. 6-Allyl-2,2-dimethyl-4-phenyl-[1,3]dioxane (**80**).* To a solution of **79** (1.10 g, 5.72 mmol) in acetone/2,2-dimethoxypropane (1:1, 20 mL) was added CSA (66 mg, 0.29 mmol, 0.05 equiv). After 14 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 1.32 g (100%) of acetonide **80** as a colorless oil and as a 70:30 mixture of *cis*/*trans* diastereomers. This compound was directly engaged in the next step without purification ($C_{15}H_{20}O_2$, MW=232.32 g mol^{-1}). IR 1642, 1378, 1198, 1167, 1100, 1070, 961, 914, 752, 697 cm^{-1}. *cis* diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.37–7.22 (m, 5H), 5.88–5.76 (m, 1H), 5.14–5.03 (m, 2H), 4.88 (dd, *J*=9.1, 2.6 Hz, 1H), 4.06–3.98 (m, 1H), 2.42–2.31 (m, 1H), 2.18 (m, 1H), 1.95 (m, 1H), 1.73 (apparent dt, *J*=13.2, 2.5 Hz, 1H), 1.55 (s, 3H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.4 (s), 133.9 (d), 128.4 (d, 2C), 127.5 (d), 125.9 (d, 2C), 117.3 (t), 99.0 (s), 71.5 (d), 68.8 (d), 40.8 (t), 38.8 (t), 30.3 (q), 19.8 (q); MS-EI *m*/*z* (relative intensity) 217 (M−Me$^+$, 49), 157 (67), 133 (54), 129 (43), 115 (63), 107 (29), 104 (41), 103 (23), 91 (54), 79 (21), 78 (21), 77 (35), 68 (43), 59 (34). trans diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.37–7.22 (m, 5H), 5.88–5.76 (m, 1H), 5.14–5.03 (m, 2H), 4.86 (dd, apparent t, *J*=4.5 Hz, 1H), 4.06–3.98 (m, 1H), 2.42–2.31 (m, 2H), 2.27 (m, 1H), 1.45–1.39 (m, 1H), 1.45 (s, 3H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.5 (s), 134.2 (d), 128.4 (d, 2C), 127.3 (d), 126.0 (d, 2C), 117.1 (t), 100.7 (s), 68.6 (d), 66.4 (d), 40.2 (t), 39.5 (t), 25.1 (q), 24.8 (q); MS-EI *m*/*z* (relative intensity) 217 (M−Me$^+$, 13), 174 (30), 162 (9), 157 (39), 133 (34), 129 (29), 115 (42), 107 (58), 106 (11), 105 (100), 104 (53), 103 (27), 91 (40), 79 (20), 78 (24), 77 (37), 68 (62), 67 (34), 59 (41), 51 (12).

*4.6.3.3. 3-(2,2-Dimethyl-6-phenyl-[1,3]dioxan-4-yl)-propan-1-ol (**81**).* To a solution of **80** (107 mg, 0.46 mmol) in THF (2 mL) at 0 °C was added dropwise a solution of $BH_3\cdot$THF (1.1 mL, 1 M in THF, 1.1 mmol, 2.5 equiv). After 1 h at 0 °C, a 3 M aqueous solution of NaOH (3 mL) and a 30% aqueous solution of H_2O_2 (3 mL) were successively added dropwise at 0 °C. After 2 h at rt, the resulting mixture was diluted with Et_2O and H_2O. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient 80:20 to 70:30) to provide 68 mg (65%) of alcohol **81** as a colorless oil and as a 70:30 mixture of cis/trans diastereomers ($C_{15}H_{22}O_3$, MW=250.33 g mol^{-1}). IR 3384, 1452, 1378, 1253, 1199, 1163, 1119, 1049, 954, 875, 753, 699 cm^{-1}. Major cis diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.38–7.24 (m, 5H), 4.90 (dd, *J*=11.6, 2.5 Hz, 1H), 4.07–3.94 (m, 1H), 3.69–3.59 (m, 2H), 2.58 (br s, 1H, OH), 1.74–1.49 (m, 6H), 1.56 (s, 3H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.2 (s), 128.4 (d, 2C), 127.6 (d), 125.9 (d, 2C), 99.1 (s), 71.5 (d), 69.3 (d), 62.6 (t), 39.2 (t), 33.1 (t), 30.1 (q), 28.7 (t), 19.7 (q); MS-EI *m*/*z* (relative intensity) 235 (M−Me$^+$, 66), 175 (55), 158 (13), 157 (100), 133 (14), 131 (12), 130 (15), 129 (78), 115 (34), 107 (39), 105 (61), 104 (76), 103 (23), 91 (33), 79 (15), 78 (21), 77 (31), 71 (80), 68 (48), 67 (18), 59 (44). Minor trans diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.38–7.24 (m, 5H), 4.87 (dd, *J*=9.6, 6.2 Hz, 1H), 4.07–3.94 (m, 1H), 3.69–3.59 (m, 2H), 2.58 (br s, 1H, OH), 2.02 (ddd, *J*=13.0, 9.6, 6.2 Hz, 1H), 1.91 (ddd, *J*=13.0, 9.0, 6.2 Hz, 1H), 1.74–1.49 (m, 4H), 1.45 (br s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.4 (s), 128.4 (d, 2C), 127.3 (d), 125.9 (d, 2C), 100.8 (s), 68.6 (d), 67.0 (d), 62.5 (t), 40.0 (t), 32.5 (t), 29.0 (t), 25.0 (q), 24.6 (q); MS-EI *m*/*z* (relative intensity) 235 (M−Me$^+$, 15), 192 (32), 175 (30), 158 (13), 157 (62), 129 (62), 115 (29), 107 (74), 105 (73), 104 (100), 103 (33), 91 (31), 78 (30), 77 (41), 71 (66), 68 (78), 59 (67).

*4.6.3.4. 5-(2-Hydroxy-2-phenylethyl)dihydrofuran-2-one (**83**).* To a solution of **81** (115 mg, 0.459 mmol) in THF/DMSO (1:1, 4 mL) was added IBX (386 mg, 1.38 mmol, 3 equiv). After 3 h at rt, H_2O (4 mL) and Et_2O (8 mL) were added and the resulting mixture was filtered through Celite (Et_2O). The layers of the filtrate were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude aldehyde was dissolved in *t*-BuOH/H_2O (7:2, 9 mL) and to the resulting solution at rt were successively added 2-methylbut-2-ene (490 μL, 4.59 mmol, 10 equiv), $NaH_2PO_4\cdot H_2O$ (790 mg, 5.05 mmol, 11 equiv), and $NaClO_2$ (250 mg, 2.76 mmol, 6 equiv). After 1.5 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NaH_2PO_4 and slightly acidified (pH <3) by dropwise addition of a 1 M aqueous solution of $KHSO_4$. After extraction with Et_2O, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude carboxylic acid **82** was treated with 80% aqueous AcOH (2 mL). After 3 h at rt, the reaction mixture was concentrated under reduced pressure and the residue was taken-up several times with toluene and evaporated

under reduced pressure. The crude material was dissolved in toluene (10 mL) and a few crystals of CSA were added. The resulting mixture was heated at reflux for 1 h and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc 50:50) and 79 mg (96%, four steps from alcohol **81**) of lactone **83** was obtained as a colorless oil and as a 70:30 mixture of diastereomers ($C_{12}H_{14}O_3$, MW=206.24 g mol^{-1}). IR 3424, 1761, 1179, 1142, 1039, 915, 760, 701, 642 cm^{-1}. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.38–7.32 (m, 5H), 4.87 (t, J=7.0 Hz, 1H), 4.38 (m, 1H), 2.75 (br s, 1H, OH), 2.55–2.40 (m, 2H), 2.35–2.24 (m, 2H), 2.00–1.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 176.9 (s), 143.3 (s), 128.7 (d, 2C), 128.1 (d), 126.0 (d, 2C), 78.6 (d), 71.8 (d), 44.6 (t), 28.5 (t), 28.2 (t). Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.38–7.32 (m, 5H), 4.94 (dd, J=9.4, 3.4 Hz, 1H), 4.84–4.79 (m, 1H), 2.75 (br s, 1H, OH), 2.55–2.40 (m, 2H), 2.35–2.24 (m, 1H), 2.00–1.80 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 177.1 (s), 144.1 (s), 128.7 (d, 2C), 127.8 (d), 125.5 (d, 2C), 77.8 (d), 70.8 (d), 45.1 (t), 28.8 (t), 28.3 (t); MS-EI m/z (relative intensity) 206 (M^+, 10), 188 ($M-H_2O^+$, 5), 133 (7), 108 (10), 107 (79), 106 (9), 105 (50), 104 (9), 103 (7), 101 (7), 100 (100), 85 (10), 82 (9), 79 (67), 78 (13), 77 (44), 58 (7), 55 (14), 51 (11).

*4.6.3.5. 5-(2-Azido-2-phenylethyl)dihydrofuran-2-one (**84**).* To a solution of benzylic alcohol **83** (35 mg, 0.17 mmol) and DPPA (73 μL, 0.34 mmol, 2 equiv) in toluene (2 mL) at 0 °C was added DBU (51 μL, 0.34 mmol, 2 equiv). After 14 h at rt the reaction mixture was hydrolyzed with H_2O (1 mL) and a 1 M solution of hydrochloric acid (1 mL). After extraction with EtOAc, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) to afford 25 mg (64%) of azide **84** as a colorless oil and a 70:30 mixture of diastereomers ($C_{12}H_{13}N_3O_2$, MW=231.25 g mol^{-1}). IR 2099, 1777, 1179, 1028, 958, 919, 763, 702 cm^{-1}. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.44–7.30 (m, 5H), 4.81–4.74 (m, 2H), 4.24–4.17 (m, 1H), 2.64–2.49 (m, 2H), 2.45–2.36 (m, 1H), 2.07–1.81 (m, 3H). Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.44–7.30 (m, 5H), 4.70 (dd, J=9.6, 5.9 Hz, 1H), 4.21 (m, 1H), 2.64–2.49 (m, 2H), 2.30–2.22 (m, 1H), 2.07–1.81 (m, 3H). ^{13}C NMR ($CDCl_3$) *only the signals corresponding to the major diastereomer could all be assigned unambiguously* δ 176.6 (s), 139.1 (s), 129.1 (d, 2C), 128.7 (d), 126.7 (d, 2C), 77.3 (d), 62.8 (d), 42.9 (t), 28.7 (t), 28.1 (t).

*4.6.3.6. Synthesis of γ-lactone **42** from azide **84**.* To a solution of azide **84** (25 mg, 0.11 mmol) in THF/H_2O (9:1, 2 mL) was added PPh_3 (31 mg, 0.12 mmol, 1.1 equiv). After 3 h at 50 °C, the reaction mixture was diluted with H_2O and Et_2O. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in pyridine (2 mL) and TsCl (23 mg, 0.12 mmol, 1.1 equiv) was added. After 48 h at rt, the reaction mixture was acidified by addition of a 4 M solution of hydrochloric acid. After extraction with EtOAc, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A 70:30 mixture of diastereomeric γ-lactones was obtained and the major diastereomer was found to be identical to γ-lactone **42** (prepared by the gold-catalyzed cyclo isomerization and Baeyer–Villiger oxidation sequence applied to ynamide **35**). The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) to afford 11.5 mg (31%) of **42** as a white solid.

4.6.4. Methyl (2R,3S*)-3-(2-oxocyclobutyl)-2-(toluene-4-sulfonylamino)propanoate (**44**)*

To a solution of **43** (114 mg, 0.371 mmol) in CH_2Cl_2 (3 mL) was added AuCl (8.0 mg, 0.037 mmol, 0.1 equiv). After 1 h at rt, the reaction mixture was hydrolyzed with a 1 M solution of hydrochloric acid and diluted with EtOAc. After 1 h stirring, the layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were successively washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 70:30+0.5% Et_3N) to afford 78 mg (65%) of cyclobutanone **44** as a colorless oil (dr=95:5) ($C_{15}H_{19}NO_5S$, MW=325.38 g mol^{-1}). IR 3266, 1775, 1740, 1597, 1495, 1435, 1339, 1206, 1158, 1090, 815, 662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J=8.2 Hz, 2H), 7.27 (d, J=8.2 Hz, 2H), 5.61 (d, J=9.4 Hz, 1H, NH), 4.08 (ddd, J=9.4, 7.5, 4.7 Hz, 1H), 3.49 (s, 3H), 3.48–3.37 (m, 1H), 3.08 (dddd, J=18.0, 10.7, 8.4, 2.3 Hz, 1H), 2.88 (dddd, J=18.0, 9.4, 4.6, 2.7 Hz, 1H), 2.40 (s, 3H), 2.23 (dddd, apparent qd, J=10.7, 4.6 Hz, 1H), 2.07 (ddd, J=14.2, 7.8, 4.7 Hz, 1H), 1.85 (ddd, apparent dt, J=14.2, 7.5 Hz, 1H), 1.68–1.59 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 210.0 (s), 171.4 (s), 143.6 (s), 136.7 (s), 129.6 (d, 2C), 127.2 (d, 2C), 56.2 (d), 54.2 (d), 52.5 (q), 44.7 (t), 32.7 (t), 21.5 (q), 16.9 (t); MS-EI m/z (relative intensity) 325 (M^+, 1), 297 (15), 266 (18), 242 (27), 238 (8), 224 (11), 174 (8), 170 (28), 155 (99), 142 (17), 94 (12), 92 (11), 91 (100), 88 (9), 65 (18), 55 (17). Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89; N, 4.30. Found: C, 55.46; H, 5.73; N, 4.23.

4.6.5. Methyl (2R,3S*)-3-(5-oxotetrahydrofuran-2-yl)-2-(toluene-4-sulfonylamino)propanoate (**45**)*

This compound was prepared by Baeyer–Villiger oxidation of cyclobutanone **44** (10 mg, 0.030 mmol) with AcOOH (25 μL, 32% in AcOH, 0.12 mmol, 4 equiv) in the presence of $AcONa\cdot 3H_2O$ (5 mg, 0.04 mmol, 1.2 equiv) in AcOH (1 mL). After 12 h at rt, work-up and purification by flash chromatography on silica gel (petroleum ether/EtOAc 50:50 to 30:70) provided 7 mg (67%) of lactone **45** as a white oil ($C_{15}H_{19}NO_6S$, MW=341.38 g mol^{-1}). IR 3281, 1775, 1724, 1453, 1430, 1336, 1154, 1091, 1058, 812, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 5.29 (d, J=9.6 Hz, 1H, NH), 4.72–4.64 (m, 1H), 4.13 (ddd, apparent td, J=9.6, 3.5 Hz, 1H), 3.51 (s, 3H), 2.57–2.50 (m, 2H), 2.42 (s, 3H), 2.41–2.33 (m, 1H), 2.10–2.04 (m, 1H), 1.90–1.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 176.1 (s), 171.5 (s), 144.0 (s), 136.2 (s), 129.7 (d, 2C), 127.4 (d, 2C), 76.6 (d), 53.3 (d), 52.8 (q), 39.6 (t), 28.7 (t), 28.1 (t), 21.6 (q); MS-EI m/z (relative intensity) 341 (M^+, 3), 283 (15), 282 ($M-CO_2Me^+$, 100), 236 (8), 198 (23), 155 (58), 110 (21), 91 (79), 85 (38), 65 (14). Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.11; H, 5.84; N, 3.74.

4.6.6. N-[(2S)-3-Benzyloxy-2-((2S*)-2-oxocyclobutyl)propyl]-4-methylbenzenesulfonamide (**46**)*

According to the representative procedure (see Section 4.6.1), the gold-catalyzed cycloisomerization of ynamide **36** (136 mg, 0.310 mmol) with AuCl (14 mg, 0.062 mmol, 0.2 equiv) in CH_2Cl_2 (5 mL) (72 h at rt) led, after purification by flash chromatography on silica gel (petroleum ether/EtOAc 75:25, 70:30), to 66 mg (55%) of cyclobutanone **46** (55%) as a colorless oil and as a 90:10 inseparable mixture of diastereomers ($C_{21}H_{25}NO_4S$, MW=387.49 g mol^{-1}). IR 3277, 1771, 1597, 1327, 1156, 1089, 1027, 814, 737, 698, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$) *only the signals corresponding to the major diastereomer could all be assigned unambiguously* δ 7.52 (d, J=8.3 Hz, 2H), 7.20–7.00 (m, 7H), 5.39 (t, J=6.2 Hz, 1H, NH), 4.25 (d, AB syst, J=11.9 Hz, 1H), 4.21 (d, AB syst, J=11.9 Hz, 1H), 3.25 (dd, J=9.5, 4.0 Hz, 1H), 3.16 (dd, J=9.5, 6.1 Hz, 1H), 3.13–3.04 (m, 1H), 2.97–2.86 (m, 2H), 2.86–2.74 (m, 1H), 2.62 (dddd, J=17.8, 9.5, 4.6, 2.6 Hz, 1H), 2.21 (s, 3H), 1.92–1.80 (m, 2H), 1.56–1.43 (m, 1H); ^{13}C NMR ($CDCl_3$) *only the signals corresponding to the major diastereomer could all be assigned unambiguously* δ 210.8 (s), 143.1 (s), 137.7 (s), 137.0 (s), 129.6 (d, 2C), 128.4 (d, 2C), 127.8 (d), 127.6 (d, 2C), 127.0 (d, 2C), 73.1 (t), 69.6 (t), 60.0 (d), 44.1 (t), 44.0 (t), 39.5 (d), 21.4 (q), 15.0 (t); MS-

EI *m/z* (relative intensity) 296 (M−Bn^+, 2), 281 (M−$BnOH^+$, 3), 266 (M−CH_2OBn^+, 2), 232 (18), 207 (5), 184 (11), 155 (32), 92 (11), 91 (100), 65 (8); HRMS calcd for $C_{21}H_{26}NO_4S$ ($M+H^+$): 388.1583, found: 388.1579.

4.6.7. *N-[(2S*)-3-Benzyloxy-2-((2S*)-2-oxotetrahydrofuran-3-yl)propyl]-4-methylbenzenesulfonamide (**47**)*

According to the representative procedure (see Section 4.6.2), ynamide **36** (450 mg, 1.02 mmol) underwent a gold-catalyzed cycloisomerization with AuCl (36 mg, 0.15 mmol, 0.15 equiv) in CH_2Cl_2 (5 mL). After 72 h at rt and work-up, the crude cyclobutanone **46** was subjected to a Baeyer–Villiger oxidation with AcOOH (790 μL, 32% in AcOH, 4.07 mmol, 4 equiv) in the presence of $AcONa\cdot 3H_2O$ (167 mg, 1.22 mmol, 1.2 equiv) in AcOH (5 mL). After 16 h at rt, work-up and purification by flash chromatography on silica gel (petroleum ether/EtOAc 50:50) afforded 229 mg (56%) of lactone **47** as a yellow oil and as a 90:10 inseparable mixture of diastereomers ($C_{21}H_{25}NO_5S$, MW=403.49 g mol^{-1}). IR 3274, 1769, 1598, 1454, 1328, 1184, 1156, 1091, 1018, 913, 813, 738, 699, 661 cm^{-1}; ^1H NMR ($CDCl_3$) *only the signals corresponding to the major diastereomer could all be assigned unambiguously* δ 7.71 (d, *J*=8.3 Hz, 2H), 7.38–7.24 (m, 7H), 4.99 (t, *J*=6.5 Hz, 1H, NH), 4.48 (d, AB syst, *J*=11.9 Hz, 1H), 4.46–4.42 (m, 1H), 4.42 (d, AB syst, *J*=11.9 Hz, 1H), 3.57 (dd, *J*=9.7, 4.4 Hz, 1H), 3.51 (dd, *J*=9.7, 5.3 Hz, 1H), 3.20 (ddd, *J*=13.2, 6.5, 4.6 Hz, 1H), 3.13 (ddd, apparent dt, *J*=13.2, 6.5 Hz, 1H), 2.52–2.42 (m, 2H), 2.42 (s, 3H), 2.23 (dq apparent, *J*=12.6, 6.2 Hz, 1H), 2.02–1.86 (m, 2H); ^{13}C NMR ($CDCl_3$) *only the signals corresponding to the major diastereomer could all be assigned unambiguously* δ 176.4 (s), 143.4 (s), 137.4 (s), 136.6 (s), 129.7 (d, 2C), 128.5 (d, 2C), 127.9 (d), 127.7 (d, 2C), 126.9 (d, 2C), 79.8 (d), 73.4 (t), 67.8 (t), 43.8 (d), 42.5 (t), 28.7 (t), 26.4 (t), 21.5 (q); MS-EI *m/z* (relative intensity) 312 (M−Bn^+, 1), 297 (M−$BnOH^+$, 3), 281 (M−CH_2OBn^+, 2), 248 (27), 231 (7), 184 (18), 171 (6), 155 (32), 142 (20), 127 (15), 92 (11), 91 (100), 65 (10); HRMS calcd for $C_{21}H_{26}NO_5S$ ($M+H^+$): 404.1532, found: 404.1537.

4.6.8. *Gold-catalyzed cycloisomerization of 1,6-ene-ynamide **37***

According to the representative procedure (see Section 4.6.1), the gold-catalyzed cycloisomerization of ynamide **37** (52 mg, 0.11 mmol) with AuCl (7 mg, 0.03 mmol, 0.25 equiv) in CH_2Cl_2 (5 mL) (48 h at rt) led, after work-up and purification by flash chromatography on silica gel (petroleum ether/EtOAc 85:15, 80:20), to 21 mg (47%) of a 75:25 inseparable mixture of cyclobutanone **48** and enone **49** as a yellow oil ($C_{21}H_{27}NO_3SSi$, MW=401.59 g mol^{-1}). IR 3274, 1766, 1673, 1597, 1427, 1326, 1250, 1156, 1114, 1092, 812, 773, 734, 700, 658 cm^{-1}.

N-{2-[(1*S**,2*S**)-2-(Dimethylphenylsilyl)-4-oxo-cyclobutyl]ethyl}-4-methylbenzenesulfonamide (**48**). ^1H NMR ($CDCl_3$) δ 7.69 (d, *J*=8.1 Hz, 2H), 7.52–7.45 (m, 2H), 7.42–7.34 (m, 3H), 7.28 (d, *J*=8.1 Hz, 2H), 5.24 (br s, 1H, NH), 3.05–2.90 (m, 3H), 2.83–2.76 (m, 2H), 2.41 (s, 3H), 1.72–1.60 (m, 1H), 1.57–1.48 (m, 1H), 1.31 (ddd, apparent q, *J*=9.8 Hz, 1H), 0.33 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 209.0 (s), 143.2 (s), 137.0 (s), 136.3 (s), 133.6 (d, 2C), 129.7 (d), 129.6 (d, 2C), 128.1 (d, 2C), 127.0 (d, 2C), 60.2 (d), 45.8 (t), 41.4 (t), 30.0 (t), 21.5 (q), 16.5 (d), −4.7 (q), −5.1 (q); MS-EI *m/z* (relative intensity) 386 (M−Me^+, 2), 373 (9), 318 (16), 213 (32), 211 (28), 184 (11), 155 (24), 149 (12), 137 (16), 136 (16), 135 (100), 91 (48), 65 (11).

N -[(*E*)-6-(Dimethylphenylsilyl)-4-oxohex-5-enyl]-4-methylbenzenesulfonamide (**49**). The spectral data of this compound were deduced from the analysis of the spectra of the 75:25 inseparable mixture of compounds **48** and **49**. ^1H NMR ($CDCl_3$) δ 7.70 (m, 2H), 7.52–7.27 (m, 7H), 7.15 (d, *J*=19.2 Hz, 1H), 6.46 (d, *J*=19.2 Hz, 1H), 4.75 (m, 1H, NH), 2.98–2.89 (m, 2H), 2.66 (t, *J*=6.8 Hz, 2H), 2.40 (s, 3H), 1.77 (apparent quintet, *J*=6.8 Hz, 2H), 0.42 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 199.4 (s), 145.3 (d), 143.3 (s), 143.0 (d), 136.9 (s), 136.2 (s), 133.8 (d, 2C), 129.7 (d), 129.6 (d, 2C), 128.0 (d, 2C), 127.1 (d, 2C), 42.7 (t), 36.3 (t), 23.4 (t), 21.5 (q), −3.2 (q, 2C).

4.6.9. *N-{2-[(2R*,3S*)-3-(Dimethylphenylsilyl)-5-oxotetrahydrofuran-2-yl]ethyl}-4-methylbenzenesulfonamide (**50**)*

This compound was prepared by treatment of a 75:25 mixture of cyclobutanone **48** and enone **49** (21 mg, 0.052 mmol, 0.039 mmol of **48**) with AcOOH (0.16 mL, 32% in AcOH, 0.80 mmol, 16 equiv) in the presence of $AcONa\cdot 3H_2O$ (8.5 mg, 0.062 mmol, 1.2 equiv) in AcOH (1 mL). After 72 h at rt, work-up and purification by flash chromatography on silica gel (petroleum ether/EtOAc 75:25, 70:30) afforded 12.5 mg (57%, 77% based on cyclobutanone **48**) of lactone **50** as a colorless oil ($C_{21}H_{27}NO_4SSi$, MW=417.59 g mol^{-1}). IR 3286, 1770, 1598, 1427, 1330, 1253, 1212, 1159, 1094, 947, 817, 780, 737, 703, 663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (d, *J*=8.2 Hz, 2H), 7.47–7.40 (m, 5H), 7.30 (d, *J*=8.2 Hz, 2H), 4.54 (br t, *J*=5.9 Hz, 1H, NH), 4.33 (ddd, apparent td, *J*=10.0, 2.2 Hz, 1H), 3.10–2.94 (m, 2H), 2.50 (dd, *J*=17.7, 9.1 Hz, 1H), 2.43 (s, 3H), 2.32 (dd, *J*=17.7, 12.8 Hz, 1H), 1.77–1.68 (m, 1H), 1.64–1.55 (m, 2H), 0.37 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 176.5 (s), 143.6 (s), 136.6 (s), 134.9 (s), 133.8 (d, 2C), 130.1 (d), 129.8 (d, 2C), 128.4 (d, 2C), 127.1 (d, 2C), 81.2 (d), 40.4 (t), 36.2 (t), 31.7 (t), 29.6 (d), 21.5 (q), −4.3 (q), −4.9 (q); MS-EI *m/z* (relative intensity) 402 (M−Me^+, 9), 340 (M−Ph^+, 8), 318 (26), 213 (20), 211 (18), 184 (13), 156 (23), 155 (32), 149 (8), 137 (20), 136 (16), 135 (100), 112 (9), 105 (9), 91 (42), 65 (8); HRMS calcd for $C_{21}H_{28}NO_4SSi$ ($M+H^+$): 418.1508, found: 418.1509.

4.6.10. *N-{2-[(1S*,2R*)-2-(Dimethylphenylsilyl)-4-oxocyclobutyl]ethyl}-4-methylbenzenesulfonamide (**51**)*

According to the representative procedure (see Section 4.6.1), the gold-catalyzed cycloisomerization of ynamide **38** (100 mg, 0.22 mmol) with AuCl (15 mg, 0.066 mmol, 0.3 equiv) in CH_2Cl_2 (5 mL) (48 h at rt) led, after work-up and purification by flash chromatography on silica gel (petroleum ether/EtOAc 85:15, 80:20), to 41 mg (47%) of cyclobutanone **51** as a yellow oil ($C_{21}H_{27}NO_3SSi$, MW=401.59 g mol^{-1}). IR 3274, 1763, 1597, 1427, 1327, 1251, 1156, 1111, 1091, 812, 772, 732, 701, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, *J*=8.3 Hz, 2H), 7.47–7.43 (m, 2H), 7.38–7.30 (m, 3H), 7.28 (d, *J*=8.3 Hz, 2H), 5.34 (dd, *J*=7.4, 4.3 Hz, 1H, NH), 3.52–3.42 (m, 1H), 3.27 (ddd, *J*=17.5, 12.2, 1.5 Hz, 1H), 3.03–2.95 (m, 1H), 2.80–2.71 (m, 2H), 2.41 (s, 3H), 2.02 (ddd, apparent td, *J*=12.2, 6.0 Hz, 1H), 1.71–1.59 (m, 1H), 1.57–1.48 (m, 1H), 0.29 (s, 3H), 0.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 210.5 (s), 143.1 (s), 137.3 (s), 137.1 (s), 133.5 (d, 2C), 129.6 (d, 2C), 129.4 (d), 128.0 (d, 2C), 127.0 (d, 2C), 60.1 (d), 45.8 (t), 42.0 (t), 28.0 (t), 21.4 (q), 14.4 (d), −3.2 (q), −3.8 (q); MS-EI *m/z* (relative intensity) 386 (M−Me^+, 4), 373 (8), 371 (5), 318 (15), 213 (34), 211 (28), 184 (11), 155 (22), 149 (10), 137 (12), 136 (14), 135 (100), 91 (36), 78 (22), 77 (10).

4.6.11. *N-{2-[(2R*,3R*)-3-(Dimethylphenylsilyl)-5-oxotetrahydrofuran-2-yl]ethyl}-4-methylbenzenesulfonamide (**52**)*

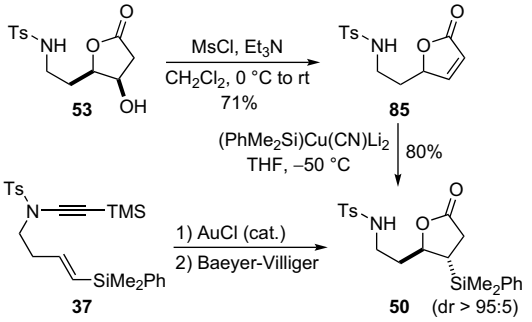
This compound was prepared by Baeyer–Villiger oxidation of cyclobutanone **51** (13 mg, 0.032 mmol) with AcOOH (50 μL, 32% in AcOH, 1.6 mmol, 8 equiv) in the presence of $AcONa\cdot 3H_2O$ (5 mg, 0.04 mmol, 1.2 equiv) in AcOH (1 mL). After 16 h at rt, work-up and purification by filtration through a short plug of silica gel (petroleum ether/EtOAc 70:30) afforded 8.3 mg (62%) of lactone **52** as a colorless oil ($C_{21}H_{27}NO_4SSi$, MW=417.59 g mol^{-1}). IR 3274, 1771, 1598, 1428, 1330, 1256, 1160, 1111, 1094, 818, 738, 704, 663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, *J*=8.3 Hz, 2H), 7.47–7.35 (m, 5H), 7.29 (d, *J*=8.3 Hz, 2H), 4.72–4.65 (m, 2H, 1H+NH), 3.04–2.95 (m, 2H), 2.48 (dd, *J*=17.4, 8.9 Hz, 1H), 2.42 (s, 3H), 2.37 (dd, *J*=17.4, 12.2 Hz, 1H), 2.20–2.12 (m, 1H), 1.75–1.67 (m, 1H), 1.59–1.49 (m, 1H), 0.36 (s, 3H), 0.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.9 (s), 143.6 (s), 136.7 (s), 135.8 (s), 133.6 (d, 2C), 129.9 (d), 129.8 (d, 2C), 128.3 (d, 2C), 127.1 (d, 2C), 81.4 (d), 40.5 (t), 33.6 (t), 29.9 (t), 28.3 (d), 21.5 (q), −3.4 (q), −3.7 (q).

4.6.12. N-{2-[(2R,3R*)-3-Hydroxy-5-oxotetrahydrofuran-2-yl]ethyl}-4-methylbenzenesulfonamide (**53**)*

Ynamide **38** (81 mg, 0.18 mmol) was subjected to a gold-catalyzed cycloisomerization with AuCl (10 mg, 0.044 mmol, 0.25 equiv) in CH_2Cl_2 (2 mL). After 72 h at rt and work-up, the crude cyclobutanone **51** was dissolved in AcOH (1 mL) and to the resulting solution were successively added AcONa (44 mg, 0.55 mmol, 3.3 equiv), KBr (44 mg, 0.37 mmol, 2.1 equiv), and AcOOH (4.3 mL, 32% in AcOH, 22.2 mmol, 125 equiv). After 16 h at rt, the reaction mixture was diluted with EtOAc, cooled to 0–5 °C, and hydrolyzed with a 25% aqueous solution of $Na_2S_2O_3$ (20 mL). After addition of H_2O, the layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were successively washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 30:70) to afford 15 mg (26%) of lactone **53** as a yellow oil ($C_{13}H_{17}NO_5S$, MW=299.34 g mol^{-1}). IR 3480, 3275, 1759, 1597, 1421, 1322, 1154, 1091, 815, 704, 663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, *J*=8.3 Hz, 2H), 7.32 (d, *J*=8.3 Hz, 2H), 5.33 (t, *J*=6.2 Hz, 1H, NH), 4.54–4.47 (m, 2H), 3.18 (br s, 1H, OH), 3.09 (td, apparent q, *J*=6.5 Hz, 2H), 2.81 (dd, *J*=17.8, 5.5 Hz, 1H), 2.54 (apparent d, *J*=17.8 Hz, 1H), 2.43 (s, 3H), 2.04 (td, apparent q, *J*=6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 176.1 (s), 143.8 (s), 136.1 (s), 129.9 (d, 2C), 127.1 (d, 2C), 82.8 (d), 68.7 (d), 40.0 (t), 39.1 (t), 28.6 (t), 21.5 (q); MS-EI *m*/*z* (relative intensity) 281 (M−H_2O^+, 22), 239 (7), 156 (11), 155 (43), 139 (4), 126 (52), 106 (6), 92 (23), 91 (100), 89 (7), 84 (27), 80 (11), 68 (6), 65 (22), 56 (6).

*4.6.13. Chemical correlation for the attribution of the relative configuration of lactones **50** and **52***

The β-hydroxylactone **53** was dehydrated (MsCl, Et_3N, CH_2Cl_2, 0 °C to rt) and the resulting γ-substituted α,β-unsaturated γ-lactone **85** (71%) underwent a highly diastereoselective silylcupration [$(PhMe_2Si)_2Cu(CN)Li_2$, THF, −50 °C] leading to the *trans*-β-silyllactone **50** (80%, dr >95:5).[44] The same compound was obtained from ynamide **37**, bearing a (*E*)-alkenyl silane, by a gold-catalyzed cycloisomerization followed by a Baeyer–Villiger oxidation.



*4.6.13.1. 4-Methyl-N-[2-(5-oxo-2,5-dihydrofuran-2-yl)ethyl]benzenesulfonamide (**85**).* To a solution of γ-hydroxylactone **53** (15 mg, 0.050 mmol) and Et_3N (20 μL, 0.15 mmol, 3 equiv) in CH_2Cl_2 (2 mL) at 0 °C was added MsCl (62 μL, 0.080 mmol, 1.6 equiv). After 2 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 50:50, 40:60) to afford 10 mg (71%) of α,β-unsaturated γ-lactone **85** as a colorless oil ($C_{13}H_{15}NO_4S$, MW=281.33 g mol^{-1}). IR 3270, 1751, 1598, 1420, 1328, 1159, 1093, 816, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, *J*=8.2 Hz, 2H), 7.48 (dd, *J*=5.6, 1.5 Hz, 1H), 7.31 (d, *J*=8.2 Hz, 2H), 6.10 (dd, *J*=5.6, 2.0 Hz, 1H), 5.14 (m, 1H), 4.92 (br t, *J*=6.2 Hz, 1H, NH), 3.22–3.05 (m, 2H), 2.43 (s, 3H), 2.14–2.06 (m, 1H), 1.76–1.68 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 172.6 (s), 156.0 (d), 143.8 (s), 136.4 (s), 129.9 (d, 2C), 127.1 (d, 2C), 121.7 (d), 80.9 (d), 39.6 (t), 33.5 (t), 21.5 (q); MS-EI *m*/*z* (relative intensity) 281 (M$^+$, 22), 239 (6), 156 (11), 126 (53), 106 (6), 92 (23), 91 (100), 89 (6), 84 (27), 80 (10), 68 (6), 65 (20), 56 (6).

*4.6.13.2. Synthesis of γ-lactone **50** by silylcupration of the α,β-unsaturated γ-lactone **85**.* To a suspension of lithium pieces (21 mg, 3.0 mmol) in THF (2 mL) at 0 °C was added chlorodimethylphenylsilane (0.17 mL, 1.0 mmol). The reaction flask was placed in an ultrasound bath for 15 min to initiate the reaction and then stirred at 0 °C. After 16 h, the resulting organosilyllithium reagent ($PhMe_2SiLi$) was cannulated into a suspension of CuCN (45 mg, 0.50 mmol) in THF (2.5 mL) at −50 °C. After 30 min at −50 °C, the resulting silylcyanocuprate solution ($(PhMe_2Si)_2Cu(CN)Li_2$) was cannulated into a solution of the α,β-unsaturated γ-lactone **85** (10 mg, 0.035 mmol) in THF (2 mL) at −50 °C. After 2 h at −50 °C, the reaction mixture was poured into a mixture of a saturated aqueous solution of NH_4Cl and a 28% aqueous solution of NH_4OH (pH=8). The resulting mixture was stirred until it became homogeneous and was then extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20, 70:30) to afford 13 mg (80%) of lactone **50**.

4.6.14. N-{(R)-2-[(1R*,2S*)-2-(tert-Butyldimethylsilyloxymethyl)-4-oxocyclobutyl]-1-phenylethyl}-4-methylbenzenesulfonamide (**54**)*

According to the representative procedure (see Section 4.6.1), the gold-catalyzed cycloisomerization of ynamide **39** (15 mg, 0.028 mmol) with AuCl (1 mg, 0.002 mmol, 0.1 equiv) in CH_2Cl_2 (1 mL) (16 h at rt) led, after work-up and purification by flash chromatography on silica gel (petroleum ether/EtOAc 85:15), to 7.5 mg (55%) of cyclobutanone **54** as a colorless oil ($C_{26}H_{37}NO_4SSi$, MW=487.73 g mol^{-1}). IR 3272, 1774, 1599, 1460, 1332, 1253, 1160, 1092, 837, 814, 777, 701, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, *J*=8.5 Hz, 2H), 7.18–7.08 (m, 5H), 7.06–7.02 (m, 2H), 6.34 (d, *J*=8.4 Hz, 1H, NH), 4.62 (ddd, dt apparent, *J*=8.4, 5.2 Hz, 1H), 3.64 (dd, *J*=10.3, 4.2 Hz, 1H), 3.57 (dd, *J*=10.3, 5.2 Hz, 1H), 2.97–2.90 (m, 1H), 2.85 (ddd, *J*=17.2, 8.1, 2.4 Hz, 1H), 2.78 (ddd, *J*=17.2, 8.3, 1.9 Hz, 1H), 2.34 (s, 3H), 2.16–2.06 (m, 1H), 1.96–1.90 (m, 2H), 0.77 (s, 9H), −0.08 (s, 3H), −0.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 210.6 (s), 142.8 (s), 139.7 (s), 138.2 (s), 129.3 (d, 2C), 128.4 (d, 2C), 127.2 (d), 127.0 (d, 2C), 126.3 (d, 2C), 63.7 (t), 57.0 (d), 55.5 (d), 45.0 (t), 35.9 (t), 32.0 (d), 25.8 (q, 3C), 21.4 (q), 18.2 (s), −5.7 (q, 2C); MS-EI *m*/*z* (relative intensity) 430 (M−*t*-Bu$^+$), 332 (M−Ts$^+$, 9), 261 (16), 260 (100), 259 (14), 229 (9), 228 (34), 227 (96), 167 (11), 155 (45), 143 (17), 129 (15), 117 (10), 115 (22), 91 (72), 75 (37), 73 (42).

4.6.15. N-{(R)-2-[(2R*,3R*)-3-(tert-Butyldimethylsilyloxymethyl)-5-oxotetrahydrofuran-2-yl]-1-phenylethyl}-4-methylbenzenesulfonamide (**55**)*

According to the representative procedure (see Section 4.6.2), ynamide **39** (70 mg, 0.13 mmol) was subjected to a gold-catalyzed cycloisomerization with AuCl (2 mg, 0.006 mmol, 0.05 equiv) in CH_2Cl_2 (2 mL). After 18 h at rt and work-up, the resulting cyclobutanone **54** was subjected to a Baeyer–Villiger oxidation with AcOOH (0.11 mL, 32% in AcOH, 0.55 mmol, 4 equiv) in the presence of AcONa·3H_2O (23 mg, 0.17 mmol, 1.3 equiv) in AcOH (3 mL). After 4 h at rt, purification by flash chromatography on silica gel (petroleum ether/EtOAc 80:20, 70:30) afforded 30 mg (46%) of lactone **55** as a pale yellow solid ($C_{26}H_{37}NO_5SSi$, MW=503.73 g mol^{-1}). Mp

127 °C; IR 3189, 1744, 1335, 1208, 1160, 1112, 1095, 992, 934, 833, 813, 776, 697, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (d, J=8.2 Hz, 2H), 7.18–7.08 (m, 5H), 7.04–7.00 (m, 2H), 5.43 (d, J=8.5 Hz, 1H, NH), 4.66 (ddd, apparent td, J=8.5, 3.6 Hz, 1H), 4.28 (ddd, J=9.8, 6.6, 2.6 Hz, 1H), 3.53 (dd, J=10.3, 4.6 Hz, 1H), 3.49 (dd, J=10.3, 5.6 Hz, 1H), 2.47 (dd, J=17.5, 8.8 Hz, 1H), 2.39–2.20 (m, 1H), 2.34 (s, 3H), 2.29–2.21 (m, 1H), 2.13 (ddd, J=14.8, 8.5, 2.6 Hz, 1H), 1.95 (ddd, J=14.8, 9.8, 3.6 Hz, 1H), 0.81 (s, 9H), −0.03 (s, 3H), −0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.6 (s), 143.1 (s), 139.8 (s), 137.6 (s), 129.3 (d, 2C), 128.6 (d, 2C), 127.5 (d), 127.1 (d, 2C), 126.2 (d, 2C), 79.4 (d), 62.5 (t), 55.3 (d), 43.0 (d), 42.4 (t), 31.0 (t), 25.8 (q, 3C), 21.4 (q), 18.1 (s), −5.6 (q), −5.7 (q); MS-EI m/z (relative intensity) 446 (M−t-Bu^+, 20), 275 (10), 261 (16), 260 (100), 246 (19), 245 (75), 228 (22), 207 (10), 183 (7), 155 (46), 117 (18), 91 (54), 75 (31), 73 (19). Anal. Calcd for $C_{26}H_{37}NO_5SSi$: C, 61.99; H, 7.40; N, 2.78. Found: C, 61.72; H, 7.41; N, 2.76.

4.6.16. (1R,3R*,5S*)-5-Methyl-3-phenyl-2-(toluene-4-sulfonyl)-2-azabicyclo-[3.2.0]heptan-1-ol (**56**) and 4-methyl-N-[(R*)-2-((1S*)-1-methyl-2-oxocyclobutyl)-1-phenylethyl]benzenesulfonamide (**57**)*

According to the representative procedure (see Section 4.6.1), the gold-catalyzed cycloisomerization of ynamide **40** (99 mg, 0.24 mmol) with AuCl (8.4 mg, 0.036 mmol, 0.15 equiv) in CH_2Cl_2 (7 mL) (30 h at rt) led, after work-up and purification by flash chromatography on silica gel (petroleum ether/EtOAc 85:15), to 45 mg (52%) of a 80:20 equilibrium mixture of the bicyclic hemiaminal **56** and cyclobutanone **57** as a pale brown solid ($C_{20}H_{23}NO_3S$, MW=357.47 g mol^{-1}). IR 3439, 3283, 1770, 1598, 1455, 1317, 1162, 1139, 1086, 1026, 993, 810, 763, 699, 674 cm^{-1}; MS-EI m/z (relative intensity) 339 (M−H_2O^+, 2), 330 (12), 329 (58), 261 (15), 260 (89), 202 (13), 184 (12), 174 (26), 155 (65), 144 (18), 143 (18), 129 (15), 106 (23), 104 (19), 91 (100), 77 (17), 69 (30), 65 (17).

Bicyclic hemiaminal (**56**): ^1H NMR ($CDCl_3$) δ 7.23 (d, J=8.3 Hz, 2H), 7.08–6.88 (m, 7H), 4.82 (dd, J=10.4, 6.5 Hz, 1H), 3.95 (s, 1H, OH), 2.97 (ddd, J=13.1, 9.6, 4.0 Hz, 1H), 2.53 (ddd, J=13.1, 11.2, 9.1 Hz, 1H), 2.29 (s, 3H), 2.17 (dd, J=13.0, 6.5 Hz, 1H), 1.88–1.62 (m, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.5 (s), 138.2 (s), 138.0 (s), 128.6 (d, 2C), 128.2 (d, 2C), 127.7 (d, 2C), 127.5 (d, 2C), 127.3 (d), 87.3 (s), 63.5 (d), 47.9 (s), 47.4 (t), 33.8 (t), 24.5 (t), 21.4 (q), 20.5 (q).

Cyclobutanone (**57**): ^1H NMR ($CDCl_3$) δ 7.38 (d, J=8.3 Hz, 2H), 7.08–6.88 (m, 7H), 4.95 (d, J=9.5 Hz, 1H, NH), 4.58 (ddd, apparent td, J=10.0, 4.7 Hz, 1H), 3.20–3.04 (m, 2H), 2.39–2.32 (m, 1H), 2.28 (s, 3H), 2.08 (dd, J=15.0, 10.5 Hz, 1H), 1.88–1.62 (m, 2H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 216.1 (s), 142.8 (s), 140.6 (s), 137.4 (s), 129.1 (d, 2C), 128.4 (d, 2C), 127.3 (d), 127.0 (d, 2C), 126.1 (d, 2C), 62.2 (s), 56.0 (d), 43.2 (t), 43.0 (t), 22.8 (t), 22.7 (q), 21.4 (q).

4.6.17. 4-Methyl-N-[(R)-2-((2S*)-2-methyl-5-oxotetrahydrofuran-2-yl)-1-phenylethyl]benzenesulfonamide (**58**)*

This compound was prepared by Baeyer–Villiger oxidation of the 80:20 mixture of bicyclic hemiaminal **56** and cyclobutanone **57** (20 mg, 0.056 mmol) with AcOOH (43 μL, 32% in AcOH, 0.22 mmol, 4 equiv) in the presence of $AcONa\cdot 3H_2O$ (9 mg, 0.07 mmol, 1.2 equiv) in AcOH (1 mL). After 5 d at rt, work-up and purification by flash chromatography on silica gel (petroleum ether/EtOAc 60:40) afforded 11 mg (52%) of lactone **58** as a colorless oil ($C_{20}H_{23}NO_4S$, MW=373.47 g mol^{-1}). IR 3262, 1751, 1598, 1455, 1322, 1285, 1155, 1089, 930, 812, 756, 701, 666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (d, J=8.2 Hz, 2H), 7.13–7.08 (m, 3H), 7.05 (d, J=8.2 Hz, 2H), 6.99–6.95 (m, 2H), 5.43 (d, J=8.2 Hz, 1H, NH), 4.52 (ddd, apparent td, J=8.2, 5.2 Hz, 1H), 2.60 (ddd, J=18.2, 9.6, 8.8 Hz, 1H), 2.49 (ddd, J=18.2, 9.6, 5.1 Hz, 1H), 2.32 (s, 3H), 2.28 (dd, J=14.9, 8.7 Hz, 1H), 2.24–2.15 (m, 1H), 2.05 (dd, J=14.9, 5.2 Hz, 1H), 2.05–1.99 (m, 1H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.3 (s), 143.1 (s), 140.6 (s), 137.1 (s), 129.2 (d, 2C), 128.6 (d, 2C), 127.5 (d), 127.1 (d, 2C), 126.2 (d, 2C), 85.6 (s), 55.2 (d), 47.5 (t), 32.7 (t), 28.9 (t), 26.5 (q), 21.4 (q); HRMS calcd for $C_{20}H_{24}NO_4S$ ($M+H^+$): 374.1426, found: 374.1435.

4.7. Preparation of 1,6-ene-ynamides possessing a propargylic alcohol moiety

*4.7.1. N-(But-3-enyl)-N-(3-hydroxybut-1-ynyl)-4-methylbenzenesulfonamide (**61**)*

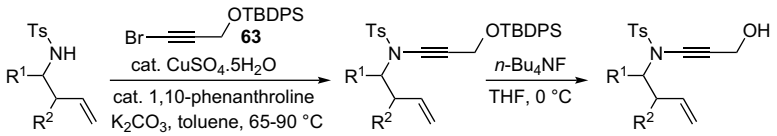
To a solution of β,β-dichloroenamide **60**[8,9] (641 mg, 2.00 mmol) in THF (10 mL) at −78 °C was added dropwise a solution of n-BuLi (1.8 mL, 2.5 M in hexanes, 4.5 mmol, 2.25 equiv). After 0.5 h at −78 °C and 1.5 h at −40 °C, freshly distilled acetaldehyde (0.60 mL, 10 mmol, 5 equiv) was added. After 0.5 h at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10, 80:20) to afford 392 mg (67%) of ynamide **61** as a yellow oil ($C_{15}H_{19}NO_3S$, MW=293.38 g mol^{-1}). IR 3377, 2242, 1642, 1597, 1358, 1166, 1089, 894, 813, 706, 678, 657 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (d, J=8.3 Hz, 2H), 7.33 (d, J=8.3 Hz, 2H), 5.68 (ddt, J=17.0, 10.3, 6.8 Hz, 1H), 5.06 (dq, J=17.0, 1.5 Hz, 1H), 5.02 (dq, J=10.3, 1.5 Hz, 1H), 4.67–4.60 (m, 1H), 3.39–3.28 (m, 2H), 2.43 (s, 3H), 2.39–2.32 (m, 3H, 2H+OH), 1.44 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.6 (s), 134.4 (s), 133.5 (d), 129.7 (d, 2C), 127.6 (d, 2C), 117.7 (t), 77.1 (s), 73.1 (s), 58.4 (d), 50.5 (t), 32.1 (t), 24.3 (q), 21.6 (q). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.32; H, 6.71; N, 4.53.

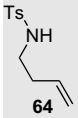
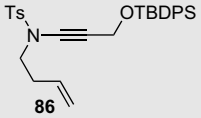
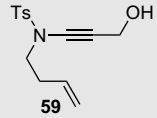
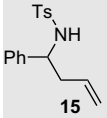
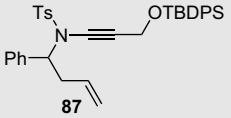
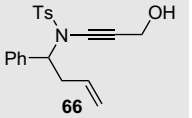
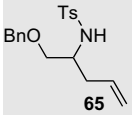
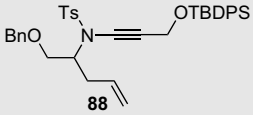
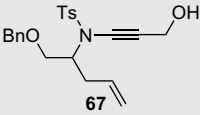
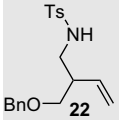
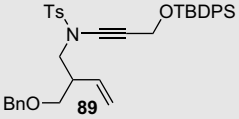
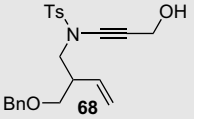
*4.7.2. N-(But-3-enyl)-N-(3-hydroxy-4-methylpent-1-ynyl)-4-methylbenzenesulfonamide (**62**)*

This compound has been prepared by treatment of a solution of β,β-dichloroenamide **60**[8,9] (700 mg, 2.19 mmol) in THF (11 mL) with n-BuLi (1.95 mL, 2.5 M in hexanes, 4.87 mmol, 2.22 equiv) (0.5 h at −78 °C, 1 h at −40 °C) followed by addition of freshly distilled isobutyraldehyde (0.75 mL, 11 mmol, 5 equiv) (−40 °C to 0 °C, 1 h at 0 °C). After work-up and purification by flash chromatography on silica gel (petroleum ether/EtOAc gradient 95:5 to 80:20), 633 mg (90%) of ynamide **62** was obtained as a colorless oil ($C_{17}H_{23}NO_3S$, MW=321.43 g mol^{-1}). IR 3506, 2241, 1642, 1597, 1359, 1167, 1090, 1018, 920, 865, 813, 708, 691, 657 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, J=8.3 Hz, 2H), 7.32 (d, J=8.3 Hz, 2H), 5.69 (ddt, J=17.0, 10.3, 6.8 Hz, 1H), 5.06 (dq, J=17.0, 1.5 Hz, 1H), 5.02 (dq, J=10.3, 1.5 Hz, 1H), 4.29 (dd, apparent t, J=5.3 Hz, 1H), 3.35 (t, J=7.4 Hz, 2H), 2.43 (s, 3H), 2.40–2.33 (m, 2H), 2.15 (d, J=5.3 Hz, 1H, OH), 1.92–1.84 (m, 1H), 0.97 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.6 (s), 134.5 (s), 133.5 (d), 129.7 (d, 2C), 127.5 (d, 2C), 117.7 (t), 78.4 (s), 70.9 (s), 68.0 (d), 50.6 (t), 34.7 (d), 32.1 (t), 21.6 (q), 18.1 (q), 17.4 (q). Anal. Calcd for $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36. Found: C, 63.49; H, 7.44; N, 4.36.

*4.7.3. Copper-catalyzed cross-coupling between sulfonamides **15, 22, 64, 65** and bromoalkyne **63** (see the following Table)*

*4.7.3.1. N-(But-3-enyl)-N-{3-[(tert-butyldiphenylsilyl)-oxy]prop-1-ynyl}-4-methylbenzenesulfonamide (**86**) (representative procedure).* To a solution of sulfonamide **64** (1.40 g, 6.21 mmol) and bromoalkyne **63** (2.55 g, 6.83 mmol, 1.1 equiv) in toluene (15 mL) were successively added K_2CO_3 (1.72 g, 12.4 mmol, 2 equiv), $CuSO_4\cdot 5H_2O$ (155 mg, 0.621 mmol, 0.1 equiv), and 1,10-phenanthroline (224 mg, 1.24 mmol, 0.2 equiv). After 17 h at 65 °C, the reaction mixture was diluted with $CHCl_3$ and filtered through



Sulfonamides	Products	Ene-ynamides
 **64**	 **86**	 **59**
 **15**	 **87**	 **66**
 **65**	 **88**	 **67**
 **22**	 **89**	 **68**

Celite ($CHCl_3$). The filtrate was evaporated under reduced pressure and the crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O 97:3, 95:5) to afford 2.47 g (77%) of disubstituted ynamide **86** as a yellow oil ($C_{30}H_{35}NO_3SSi$, MW=517.75 g mol^{-1}). IR 2242, 1596, 1428, 1362, 1170, 1109, 1066, 813, 739, 701, 679, 657, 611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J=8.0 Hz, 2H), 7.72–7.68 (m, 4H), 7.45–7.35 (m, 6H), 7.29 (d, J=8.0 Hz, 2H), 5.68 (ddt, J=17.1, 10.5, 6.8 Hz, 1H), 5.06 (dq, J=17.1, 1.5 Hz, 1H), 5.03 (dq, J=10.3, 1.5 Hz, 1H), 4.49 (s, 2H), 3.29 (t, J=7.5 Hz, 2H), 2.43 (s, 3H), 2.33–2.27 (m, 2H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.4 (s), 135.6 (d, 4C), 134.7 (s), 133.6 (d), 133.2 (2s, 2C), 129.7 (2d, 2C+2C), 127.7 (2d, 4C), 127.6 (d, 2C), 117.6 (t), 78.2 (s), 70.0 (s), 52.9 (t), 50.6 (t), 32.1 (t), 26.6 (q, 3C), 21.6 (q), 19.2 (s).

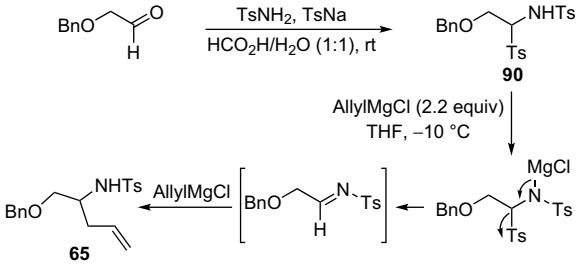
*4.7.3.2. N-But-3-enyl-N-(3-hydroxyprop-1-ynyl)-4-methylbenzenesulfonamide (**59**) (representative procedure).* To a solution of the disubstituted ynamide **86** (300 mg, 0.580 mmol) in THF (10 mL) was added a solution of n-Bu_4NF (0.75 mL, 1 M in THF, 0.75 mmol, 1.3 equiv). After 10 min at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient 90:10 to 60:40), to afford 140 mg (86%, 66% for the two steps from sulfonamide **64**) of ynamide **59** as a colorless oil ($C_{14}H_{17}NO_3S$, MW=279.35 g mol^{-1}). IR 3378, 2241, 1642, 1596, 1357, 1166, 1089, 1017, 998, 915, 854, 813, 706, 678, 658 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 5.68 (ddt, J=17.0, 10.2, 6.8 Hz, 1H), 5.07 (dq, J=17.0, 1.5 Hz, 1H), 5.02 (dq, J=10.2, 1.5 Hz, 1H), 4.38 (d, J=5.5 Hz, 2H), 3.36 (t, J=7.3 Hz, 2H), 2.43 (s, 3H), 2.42–2.31 (m, 2H), 2.06 (br t, J=5.5 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 144.7 (s), 134.6 (s), 133.5 (d), 129.8 (d, 2C), 127.5 (d, 2C), 117.7 (t), 78.8 (s), 70.0 (s), 51.1 (t), 50.6 (t), 32.1 (t), 21.6 (q); MS-EI m/z (relative intensity) 238 (M−Allyl$^+$, 5), 216 (12), 214 (13), 200 (10), 184 (11), 155 (36), 139 (13), 124 (16), 108 (10), 92 (18), 91 (100), 79 (14), 66 (19), 65 (28), 55 (77), 53 (11).

*4.7.3.3. N-[3-(tert-Butyldiphenylsilyloxy)prop-1-ynyl]-4-methyl-N-(1-phenylbut-3-enyl)benzenesulfonamide (**87**).* The coupling between sulfonamide **15** (411 mg, 1.36 mmol) and bromoalkyne **63** (610 mg, 1.63 mmol, 1.2 equiv) in the presence of $CuSO_4{\cdot}5H_2O$ (34 mg, 0.14 mmol, 0.1 equiv), 1,10-phenanthroline (49 mg, 0.27 mmol, 0.2 equiv), and K_2CO_3 (377 mg, 2.72 mmol, 2 equiv) in toluene (5 mL) (30 h at 90 °C) led, after purification by flash chromatography on silica gel (petroleum ether/EtOAc 98:2), to 157 mg (60%) of the disubstituted ynamide **87** as a colorless oil ($C_{36}H_{39}NO_3SSi$, MW=593.85 g mol^{-1}). IR 2240, 1643, 1597, 1428, 1363, 1169, 1111, 1072, 997, 823, 741, 702, 663, 609 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.71–7.68 (m, 4H), 7.51 (d, J=8.3 Hz, 2H), 7.45–7.34 (m, 6H), 7.23–7.12 (m, 5H), 7.08 (d, J=8.3 Hz, 2H), 5.57 (ddt, J=17.0, 10.2, 6.9 Hz, 1H), 5.06 (dq, J=17.0, 1.4 Hz, 1H), 4.97–4.91 (m, 2H), 4.51 (s, 2H), 2.72–2.63 (m, 1H), 2.55–2.48 (m, 1H), 2.34 (s, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.0 (s), 137.7 (s), 135.5 (d, 4C), 135.3 (s), 133.5 (d), 133.3 (2s, 2C), 129.8 (2d, 2C), 129.2 (d, 2C), 128.3 (d, 2C), 127.9 (d), 127.8 (2d, 4C), 127.7 (d, 2C), 127.1 (d, 2C), 118.3 (t), 76.4 (s), 72.8 (s), 63.0 (d), 53.1 (t), 38.3 (t), 26.6 (q, 3C), 21.6 (q), 19.2 (s); MS-EI m/z (relative intensity) 337 (M−t-$BuPh_2SiOH^+$, 28), 275 (7), 274 (26), 273 (100), 199 (28), 197 (7), 181 (6), 139 (4), 91 (8), 77 (8).

*4.7.3.4. N-(3-Hydroxyprop-1-ynyl)-4-methyl-N-(1-phenylbut-3-enyl)-benzenesulfonamide (**66**).* The disubstituted ynamide **87** (459 mg, 0.773 mmol) was desilylated [n-Bu_4NF (1.32 mL, 1 M in THF, 1.32 mmol, 1.7 equiv), THF (15 mL), 0 °C, 0.5 h] and purification by flash chromatography on silica gel (petroleum ether/EtOAc 75:25) afforded 250 mg (91%, 55% for the two steps from sulfonamide **15**) of ynamide **66** as a colorless oil ($C_{20}H_{21}NO_3S$, MW=355.45 g mol^{-1}). IR 3394, 2239, 1642, 1597, 1359, 1166, 1089, 1017, 982, 923, 813, 701,

662, 605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (d, J=8.3 Hz, 2H), 7.20–7.12 (m, 5H), 7.08 (d, J=8.2 Hz, 2H), 5.52 (ddt, J=17.0, 10.2, 6.9 Hz, 1H), 5.02 (dq, J=17.0, 1.4 Hz, 1H), 4.93–4.87 (m, 2H), 4.36 (d, J=5.6 Hz, 2H), 2.73–2.64 (m, 1H), 2.57–2.49 (m, 1H), 2.31 (s, 3H), 1.62 (br t, J=5.6 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 144.3 (s), 138.6 (s), 135.2 (s), 133.4 (d), 129.3 (d, 2C), 128.4 (d, 2C), 128.1 (d), 127.7 (d, 2C), 127.1 (d, 2C), 118.4 (t), 76.7 (s, overlap with $CDCl_3$), 72.8 (s), 62.9 (d), 51.4 (t), 38.1 (t), 21.6 (q).

*4.7.3.5. N-[1-(Benzyloxymethyl)but-3-enyl]-4-methylbenzenesulfonamide (**65**).* This sulfonamide was prepared from (benzyloxy) acetaldehyde by formation of the (sulfonamido)sulfone **90** [$TsNH_2$, TsNa, $HCOOH/H_2O$ (1:1), rt].[45] This adduct could not be converted to the corresponding unstable *N*-tosylimine **91** under the reported conditions.[45] However, treatment of compound **90** with allylmagnesium chloride (2.2 equiv, THF, −10 °C) resulted in the generation of the *N*-tosylimine **91** in situ and condensation of the Grignard reagent provided sulfonamide **65**.



A solution of (benzyloxy)acetaldehyde (560 μL, 4.00 mmol), *p*-toluenesulfonamide (685 mg, 4.00 mmol, 1 equiv), and sodium *p*-toluenesulfinate (713 mg, 4.00 mmol, 1 equiv) in a mixture of HCOOH (6 mL) and H_2O (6 mL) was stirred at rt. After 16 h, the white precipitate was collected by filtration, washed with H_2O (2×7 mL), pentane (7 mL), and dried under reduced pressure. The crystalline sulfonamidosulfone adduct was dissolved in THF (10 mL) and a solution of allylmagnesium chloride (4.4 mL, 2 M in THF, 8.8 mmol, 2.2 equiv) was added at −10 °C. After 1.5 h at −10 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were successively washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10) to afford 480 mg (ca. 35%) of sulfonamide **65** as a colorless oil. This compound showed slight contamination by unidentified impurities ($C_{19}H_{23}NO_3S$, MW=345.46 g mol^{-1}). IR 3277, 1641, 1598, 1328, 1158, 1091, 1027, 994, 914, 813, 735, 698, 663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (d, J=8.3 Hz, 2H), 7.36–7.20 (m, 7H), 5.56 (ddt, J=17.0, 9.6, 7.1 Hz, 1H), 5.02–4.96 (m, 2H), 4.89 (d, J=7.3 Hz, 1H, NH), 4.36 (s, 2H), 3.42–3.35 (m, 2H), 3.25 (dd, J=10.7, 6.4 Hz, 1H), 2.40 (s, 3H), 2.30–2.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 143.2 (s), 137.8 (s), 137.7 (s), 133.5 (d), 129.5 (d, 2C), 128.3 (d, 2C), 127.7 (d), 127.5 (d, 2C), 127.0 (d, 2C), 118.4 (t), 73.1 (t), 70.6 (t), 52.8 (d), 36.6 (t), 21.4 (q); MS-EI m/z (relative intensity) 304 ($M-Allyl^+$, 24), 225 (5), 224 (41), 190 (7), 155 (26), 92 (9), 91 (100), 65 (8), 54 (6).

*4.7.3.6. N-[1-(Benzyloxymethylbut)3-enyl]-N-[3-(tert-butyldiphenylsilyloxy)prop-1-ynyl]-4-methylbenzenesulfonamide (**88**).* The coupling between sulfonamide **65** (319 mg, 0.923 mmol) and bromoalkyne **63** (413 mg, 1.11 mmol, 1.2 equiv) in the presence of $CuSO_4 \cdot 5H_2O$ (23 mg, 0.092 mmol, 0.1 equiv), 1,10-phenanthroline (33 mg, 0.18 mmol, 0.2 equiv), and K_2CO_3 (255 mg, 1.85 mmol, 2 equiv) in toluene (5 mL) (30 h at 90 °C) led, after purification by flash chromatography on silica gel (petroleum ether/Et_2O 95:5, petroleum ether/EtOAc 95:5), to 188 mg (32%) of the disubstituted ynamide **88** as a yellow oil ($C_{38}H_{43}NO_4SSi$, MW=637.90 g mol^{-1}). IR 2238, 1462, 1362, 1170, 1112, 1079, 970, 823, 741, 703, 674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (d, J=8.5 Hz, 2H), 7.75–7.70 (m, 4H), 7.46–7.36 (m, 6H), 7.32–7.25 (m, 3H), 7.20–7.15 (m, 4H), 5.62 (ddt, J=17.0, 10.0, 7.0 Hz, 1H), 5.06 (dq, J=17.0, 1.5 Hz, 1H), 4.97 (dm, apparent br d, J=10.0 Hz, 1H), 4.51 (d, AB syst, J=16.0 Hz, 1H), 4.46 (d, AB syst, J=16.0 Hz, 1H), 4.37 (d, AB syst, J=12.0 Hz, 1H), 4.30 (d, AB syst, J=12.0 Hz, 1H), 4.22–4.16 (m, 1H), 3.43 (dd, J=10.0, 8.0 Hz, 1H), 3.38 (dd, J=10.0, 5.2 Hz, 1H), 2.37 (s, 3H), 2.33–2.18 (m, 2H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.0 (s), 137.8 (s), 135.9 (d), 135.5 (d, 4C), 134.6 (s), 133.2 (s, 2C), 129.7 (d, 2C), 129.6 (d, 2C), 128.3 (d, 2C), 127.7 (d, 4C), 127.6 (2d, 3C), 127.5 (d, 2C), 118.2 (t), 75.3 (s), 72.9 (t), 72.2 (s), 69.9 (t), 59.5 (d), 52.9 (t), 34.4 (t), 26.6 (q, 3C), 21.6 (q), 19.2 (s).

*4.7.3.7. N-[1-(Benzyloxymethyl)but-3-enyl]-N-(3-hydroxyprop-1-ynyl)-4-methylbenzenesulfonamide (**67**).* The disubstituted ynamide **88** (267 mg, 0.419 mmol) was desilylated [n-Bu_4NF (0.63 mL, 1 M in THF, 0.63 mmol, 1.5 equiv) in THF (5 mL), 0 °C, 15 min] and purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) afforded 146 mg (87%, 28% for the two steps from sulfonamide **65**) of ynamide **67** as a colorless oil ($C_{22}H_{25}NO_4S$, MW=399.50 g mol^{-1}). IR 3421, 2239, 1644, 1597, 1495, 1454, 1359, 1168, 1091, 1002, 922, 856, 814, 741, 702, 666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, J=8.3 Hz, 2H), 7.33–7.12 (m, 7H), 5.63 (ddt, J=17.0, 10.1, 7.1 Hz, 1H), 5.06 (dq, J=17.0, 1.3 Hz, 1H), 4.98 (apparent br d, J=10.1 Hz, 1H), 4.40 (d, AB syst, J=12.0 Hz, 1H), 4.36 (d, AB syst, J=16.6 Hz, 1H), 4.31 (d, AB syst, J=16.6 Hz, 1H), 4.29 (d, AB syst, J=12.0 Hz, 1H), 4.24–4.13 (m, 1H), 3.47 (dd, J=10.2, 8.1 Hz, 1H), 3.40 (dd, J=10.2, 5.0 Hz, 1H), 2.83 (s, 3H), 2.34–2.26 (m, 2H), 1.86 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 144.3 (s), 137.8 (s), 135.5 (s), 133.1 (d), 129.3 (d, 2C), 128.3 (d, 2C), 128.0 (d, 2C), 127.7 (d, 2C), 127.6 (d), 118.4 (t), 76.1 (s), 72.9 (t), 72.3 (s), 69.7 (t), 59.6 (d), 51.3 (t), 34.5 (t), 21.6 (q); HRMS calcd for $C_{22}H_{26}NO_4S$ ($M+H^+$): 400.1583, found: 400.1578.

*4.7.3.8. N-[2-(Benzyloxymethyl)but-3-enyl]-N-[3-(tert-butyldiphenylsilyloxy)prop-1-ynyl]-4-methylbenzenesulfonamide (**89**).* The coupling between sulfonamide **22** (609 mg, 1.76 mmol) and bromoalkyne **63** (723 mg, 1.94 mmol, 1.1 equiv) in the presence of $CuSO_4 \cdot 5H_2O$ (44 mg, 0.18 mmol, 0.1 equiv), 1,10-phenanthroline (64 mg, 0.35 mmol, 0.2 equiv), and K_2CO_3 (487 mg, 3.52 mmol, 2 equiv) in toluene (5 mL) (16 h at 65 °C) led, after purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5), to 1.08 g (96%) of disubstituted ynamide **89** as a viscous colorless oil ($C_{38}H_{43}NO_4SSi$, MW=637.90 g mol^{-1}). IR 2241, 1596, 1362, 1106, 1068, 921, 813, 738, 700, 653, 611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (d, J=8.2 Hz, 2H), 7.69–7.65 (m, 4H), 7.43–7.24 (m, 13H), 5.71 (ddd, J=17.4, 10.3, 8.1 Hz, 1H), 5.14–5.06 (m, 2H), 4.49 (d, AB syst, J=12.0 Hz, 1H), 4.44 (d, AB syst, J=12.0 Hz, 1H), 4.43 (s, 2H), 3.47 (dd, J=9.3, 5.4 Hz, 1H), 3.44 (dd, J=9.3, 5.4 Hz, 1H), 3.42 (dd, J=12.7, 7.1 Hz, 1H), 3.24 (dd, J=12.7, 7.8 Hz, 1H), 2.78–2.68 (m, 1H), 2.41 (s, 3H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.4 (s), 138.2 (s), 135.9 (d), 135.5 (d, 4C), 134.6 (s), 133.2 (s, 2C), 129.7 (d, 2C), 129.6 (d, 2C), 128.3 (d, 2C), 127.7 (d, 4C), 127.6 (2d, 3C), 127.5 (d, 2C), 117.9 (t), 78.6 (s), 73.1 (t), 70.5 (t), 69.8 (s), 52.8 (t), 52.6 (t), 42.6 (d), 26.6 (q, 3C), 21.6 (q), 19.1 (s); MS-EI m/z (relative intensity) 337 (27), 275 (7), 274 (26), 273 (100), 199 (23), 197 (7), 181 (6), 91 (4), 77 (7).

*4.7.3.9. N-[2-(Benzyloxymethyl)but-3-enyl]-N-(3-hydroxy-prop-1-ynyl)-4-methylbenzenesulfonamide (**68**).* The disubstituted ynamide **89** (1.01 g, 1.59 mmol) was desilylated [n-Bu_4NF (2.5 mL, 1 M in THF, 2.5 mmol, 1.6 equiv) in THF (10 mL), 0 °C, 0.5 h] and purification by flash chromatography on silica gel (petroleum ether/EtOAc gradient 80:20 to 60:40) afforded 574 mg (91%, 87% for the two steps from sulfonamide **22**) of ynamide **68** as a colorless oil ($C_{22}H_{25}NO_4S$, MW=399.50 g mol^{-1}). IR 3406, 2241, 1596, 1454, 1360, 1167, 1090, 1005, 923, 814, 738, 700, 655 cm^{-1}; ^1H

NMR ($CDCl_3$) δ 7.78 (d, J=8.3 Hz, 2H), 7.36–7.26 (m, 7H), 5.73 (ddd, J=17.4, 10.3, 8.1 Hz, 1H), 5.15 (d, J=17.4 Hz, 1H), 5.12 (d, J=10.3 Hz, 1H), 4.50 (d, AB syst, J=12.0 Hz, 1H), 4.46 (d, AB syst, J=12.0 Hz, 1H), 4.34 (d, J=5.3 Hz, 2H), 3.54–3.44 (m, 3H), 3.33 (dd, J=12.7, 7.9 Hz, 1H), 2.86–2.75 (m, 1H), 2.44 (s, 3H), 1.10 (br t, J=5.3 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 144.7 (s), 138.2 (s), 135.8 (d), 134.5 (s), 129.8 (d, 2C), 128.4 (d, 2C), 127.7 (d), 127.6 (2d, 4C), 118.1 (t), 79.4 (s), 73.1 (t), 70.6 (t), 69.8 (s), 52.7 (t), 51.2 (t), 42.8 (d), 21.7 (q).

4.8. Gold-catalyzed cycloisomerizations of 1,6-ene-ynamides possessing a propargylic alcohol moiety

4.8.1. (1R,5R*)-[2-(4-Methylbenzenesulfonyl)-2-azabicyclo-[3.1.0]hex-1-yl]ethanal (**69**) (representative procedure)*

To a solution of ynamide **59** (70 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added AuCl (2.9 mg, 0.012 mmol, 0.05 equiv). After 20 min at rt, the reaction mixture was filtered through a short plug of Celite. The filtrate was evaporated and the crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) to afford 28 mg (40%) of aldehyde **69** as a colorless oil ($C_{14}H_{17}NO_3S$, MW=279.35 g mol^{-1}). IR 1724, 1597, 1336, 1159, 1088, 1037, 911, 815, 730, 709, 657 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.98 (apparent t, J=1.5 Hz, 1H), 7.71 (d, J=8.0 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 3.68 (apparent dt, J=17.0, 1.5 Hz, 1H), 3.60 (apparent td, J=10.5, 1.5 Hz, 1H), 2.60 (ddd, apparent td, J=10.5, 8.0 Hz, 1H), 2.44 (s, 3H), 2.34 (dd, J=17.0, 1.5 Hz, 1H), 2.22–2.12 (m, 1H), 1.78 (dd, J=12.5, 8.0 Hz, 1H), 1.46 (apparent dt, J=8.5, 5.5 Hz, 1H), 0.49 (dd, J=8.5, 6.5 Hz, 1H), 0.47 (dd, J=6.5, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 200.9 (d), 144.0 (s), 132.5 (s), 129.5 (d, 2C), 128.5 (d, 2C), 47.6 (t), 46.9 (t), 43.2 (s), 24.2 (t), 23.2 (d), 21.6 (q), 12.1 (t); MS-EI m/z (relative intensity) 251 (M−CO$^+$ or M−$C_2H_4^+$, 15), 187 (29), 186 (48), 172 (7), 155 (Ts$^+$, 12), 131 (7), 124 (M−Ts$^+$, 64), 105 (17), 96 (34), 95 (7), 94 (11), 92 (10), 91 (100), 89 (7), 82 (7), 65 (25), 56 (7), 55 (100), 54 (8), 53 (9).

4.8.2. {(1R,5R*)-1-[2-(4-Methylbenzenesulfonyl)-2-azabicyclo[3.1.0]hex-1-yl]}propan-2-one (**70**)*

The gold-catalyzed cycloisomerization of ynamide **61** (80 mg, 0.27 mmol) with AuCl (3.1 mg, 0.013 mmol, 0.05 equiv) in CH_2Cl_2 (3 mL) (0.5 h at rt) afforded, after purification by flash chromatography on silica gel (petroleum ether/EtOAc 75:25), 48 mg (60%) of ketone **70** as a colorless oil ($C_{15}H_{19}NO_3S$, MW=293.38 g mol^{-1}). IR 1715, 1597, 1334, 1159, 1088, 1042, 816, 711, 659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J=8.2 Hz, 2H), 7.32 (d, J=8.2 Hz, 2H), 3.78 (d, AB syst, J=16.7 Hz, 1H), 3.58 (ddd, apparent td, J=10.0, 1.3 Hz, 1H), 2.56 (ddd, apparent td, J=10.0, 8.0 Hz, 1H), 2.43 (s, 3H), 2.28 (d, AB syst, J=16.7 Hz, 1H), 2.26 (s, 3H), 2.24–2.13 (m, 1H), 1.72 (dd, J=12.3, 7.8 Hz, 1H), 1.46 (apparent dt, J=8.8, 5.2 Hz, 1H), 0.45 (dd, J=8.8, 6.5 Hz, 1H), 0.03 (dd, apparent t, J=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 206.5 (s), 143.8 (s), 132.7 (s), 129.4 (d, 2C), 128.5 (d, 2C), 47.8 (t), 46.6 (t), 43.9 (s), 31.1 (q), 24.2 (t), 23.4 (d), 21.5 (q), 12.3 (t); MS-EI m/z (relative intensity) 293 (M$^+$, 1), 155 (5), 139 (11), 138 (100), 97 (4), 96 (49), 95 (4), 94 (5), 91 (24), 65 (9), 55 (45). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.12; H, 6.53; N, 4.45.

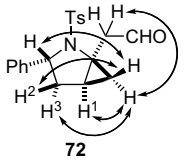
4.8.3. {(1R,5R*)-3-Methyl-1-[2-(4-methylbenzenesulfonyl)-2-azabicyclo[3.1.0]hex-1-yl]}butan-2-one (**71**)*

The gold-catalyzed cycloisomerization of ynamide **62** (152 mg, 0.473 mmol) with AuCl (5.5 mg, 0.024 mmol, 0.05 equiv) in CH_2Cl_2 (4 mL) (35 min at rt) afforded, after purification by flash chromatography on silica gel (petroleum ether/EtOAc 98:2, 95:5), 64 mg (42%) of ketone **71** as a colorless oil ($C_{17}H_{23}NO_3S$, MW=321.43 g mol^{-1}). IR 1714, 1597, 1335, 1160, 1089, 1036, 945, 814, 782, 710, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J=8.2 Hz, 2H), 7.31 (d, J=8.2 Hz, 2H), 3.91 (d, AB syst, J=16.7 Hz, 1H), 3.58 (apparent td, J=10.0, 1.7 Hz, 1H), 2.75 (apparent septet, J=7.0 Hz, 1H), 2.58 (ddd, apparent td, J=10.0, 8.1 Hz, 1H), 2.45 (s, 3H), 2.32 (d, AB syst, J=16.7 Hz, 1H), 2.28–2.19 (m, 1H), 1.72 (dd, J=12.4, 7.8 Hz, 1H), 1.46 (ddd, apparent dt, J=8.6, 5.3 Hz, 1H), 1.12 (d, J=7.0 Hz, 6H), 0.45 (dd, J=8.6, 6.5 Hz, 1H), 0.03 (dd, apparent t, J=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 211.8 (s), 143.7 (s), 133.0 (s), 129.4 (d, 2C), 128.5 (d, 2C), 48.1 (t), 43.9 (t), 43.7 (s), 41.1 (d), 24.4 (t), 23.6 (d), 21.5 (q), 18.0 (q), 17.7 (q), 12.5 (t); MS-EI m/z (relative intensity) 321 (M$^+$, 1), 278 (M−i-Pr$^+$, 3), 186 (5), 167 (12), 166 (100), 155 (7), 96 (40), 96 (49), 91 (21), 71 (17), 65 (6), 55 (29).

4.8.4. [(1R,3R*,5R*)-3-Phenyl-2-(4-methylbenzenesulfonyl)-2-azabicyclo-[3.1.0]hex-1-yl]ethanal (**72**)*

The gold-catalyzed cycloisomerization of ynamide **66** (127 mg, 0.357 mmol) with AuCl (4 mg, 0.02 mmol, 0.05 equiv) in CH_2Cl_2 (3 mL) (1 h at rt) afforded, after purification by flash chromatography on silica gel (petroleum ether/EtOAc gradient 90:10 to 70:30), 78 mg (61%) of aldehyde **72** as a colorless oil ($C_{20}H_{21}NO_3S$, MW=355.45 g mol^{-1}). IR 1726, 1597, 1493, 1450, 1340, 1160, 1085, 1029, 961, 812, 760, 729, 699, 657 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.96 (t, J=1.6 Hz, 1H), 7.45 (br d, J=8.1 Hz, 2H), 7.18–7.10 (m, 5H), 7.12 (br d, J=8.1 Hz, 2H), 4.12 (dd, apparent t, J=8.8 Hz, 1H), 3.83 (apparent br d, J=17.4 Hz, 1H), 2.33 (dd, J=17.4, 1.6 Hz, 1H), 2.31 (s, 3H), 2.27 (dd, J=13.1, 8.8 Hz, 1H), 2.16 (ddd, J=13.1, 8.8, 5.5 Hz, 1H), 1.42 (apparent dt, J=8.8, 5.5 Hz, 1H), 0.61 (dd, J=8.8, 6.6 Hz, 1H), 0.47 (dd, J=6.6, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 200.8 (d), 143.8 (s), 141.6 (s), 134.3 (s), 129.3 (d, 2C), 128.4 (d, 2C), 128.3 (d, 2C), 127.3 (d), 126.8 (d, 2C), 65.0 (d), 48.1 (t), 45.1 (s), 37.8 (t), 21.9 (d), 21.5 (q), 14.9 (t); MS-EI m/z (relative intensity) 355 (M$^+$, 1), 327 (2), 263 (32), 262 (20), 200 (51), 172 (26), 155 (15), 132 (16), 131 (78), 129 (16), 117 (19), 116 (16), 105 (21), 104 (21), 103 (16), 91 (100), 77 (11), 65 (14); HRMS calcd for $C_{20}H_{22}NO_3S$ (M+H$^+$): 356.1320, found: 356.1326.

Relevant NOESY correlations (500 MHz, $CDCl_3$)



72

4.8.5. [(1R,3R*,5R*)-3-Benzyloxymethyl-2-(4-methylbenzenesulfonyl)-2-azabicyclo[3.1.0]hex-1-yl]acetaldehyde (**73**)*

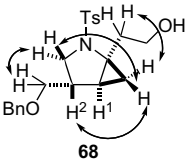
The gold-catalyzed cycloisomerization of ynamide **67** (73 mg, 0.18 mmol) with AuCl (2 mg, 0.009 mmol, 0.05 equiv) in CH_2Cl_2 (3 mL) (0.5 h at rt) afforded, after purification by flash chromatography on silica gel (petroleum ether/EtOAc: 80:20), 37 mg (51%) of aldehyde **73** as a colorless oil ($C_{22}H_{25}NO_4S$, MW=399.50 g mol^{-1}). IR 1723, 1597, 1494, 1453, 1342, 1159, 1089, 1042, 815, 737, 698, 665, 594 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.92 (dd, J=2.3, 1.5 Hz, 1H), 7.71 (d, J=8.4 Hz, 2H), 7.39–7.28 (m, 7H), 4.55 (d, AB syst, J=11.9 Hz, 1H), 4.50 (d, AB syst, J=11.9 Hz, 1H), 3.71 (dd, J=8.6, 3.3 Hz, 1H), 3.67–3.60 (m, 1H), 3.57 (dd, J=8.6, 7.3 Hz, 1H), 3.53 (dd, J=17.2, 1.5 Hz, 1H), 2.44 (s, 3H), 2.33 (dd, J=17.2, 2.3 Hz, 1H), 2.30–2.23 (m, 1H), 1.91 (apparent dd, J=13.2, 8.5 Hz, 1H), 1.52–1.46 (m, 1H), 0.70 (ddd, J=8.8, 6.0, 0.8 Hz, 1H), 0.17 (dd, apparent br t, J=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 201.2 (d), 144.0 (s), 138.1 (s), 134.9 (s), 129.6 (d, 2C), 128.4 (d, 2C), 128.3 (d, 2C), 127.8 (d, 2C), 127.7 (d), 73.5 (2t, 2C), 63.3 (d), 48.2 (t), 46.0 (s), 31.5 (t), 22.8 (d), 21.6 (q), 19.6 (t). Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 65.71; H, 6.49; N, 3.52.

4.8.6. [(1R,4S*,5S*)-3-Benzyloxymethyl-2-(4-methylbenzenesulfonyl)-2-azabicyclo[3.1.0]hex-1-yl]ethanol (**74**)*

To a solution of ynamide **68** (488 mg, 1.22 mmol) in CH_2Cl_2 (10 mL) was added AuCl (14 mg, 0.060 mmol, 0.05 equiv). After 0.5 h, the reaction mixture was filtered through Celite (CH_2Cl_2). The

filtrate was evaporated under reduced pressure and the crude material was dissolved in MeOH (5 mL). To the resulting solution at 0 °C was added $NaBH_4$ (92 mg, 2.4 mmol, 2 equiv). After 1 h at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and MeOH was evaporated under reduced pressure. The residue was extracted with EtOAc, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc 50:50) to afford 297 mg (60%) of alcohol **74** as a yellow oil and as a 90:10 mixture of diastereomers ($C_{22}H_{27}NO_4S$, MW=401.52 g mol^{-1}). IR 3246, 1597, 1494, 1453, 1336, 1160, 1088, 1038, 815, 736, 699, 672 cm^{-1}; ^{1}H NMR ($CDCl_3$) *only the signals corresponding to the major diastereomer could all be assigned unambiguously* δ 7.82 (d, J=8.4 Hz, 2H), 7.50–7.40 (m, 7H), 4.75 (d, AB syst, J=12.2 Hz, 1H), 4.65 (d, AB syst, J=12.2 Hz, 1H), 4.30–4.22 (m, 1H), 3.90 (apparent dt, J=11.5, 4.5 Hz, 1H), 3.66 (dd, J=9.3, 4.7 Hz, 1H), 3.60 (dd, apparent br d, J=10.5 Hz, 1H), 3.51 (dd, J=9.3, 4.7 Hz, 1H), 3.03 (ddd, apparent dt, J=14.8, 3.7 Hz, 1H), 2.91 (dd, J=10.5, 8.4 Hz, 1H), 2.57 (s, 3H), 2.38–2.32 (m, 1H), 1.53 (dd, J=8.9, 5.0 Hz, 1H), 1.42 (ddd, J=14.8, 9.6, 5.0 Hz, 1H), 0.42 (dd, J=8.9, 6.4 Hz, 1H), 0.00 (dd, J=6.4, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) *only the signals corresponding to the major diastereomer could all be assigned unambiguously* δ 143.9 (s), 137.2 (s), 132.5 (s), 129.4 (d, 2C), 128.5 (2d, 4C), 127.6 (d, 2C), 127.4 (d), 73.5 (t), 72.1 (t), 59.6 (t), 51.6 (t), 45.7 (s), 37.9 (d), 36.7 (t), 25.6 (d), 21.5 (q), 12.0 (t); MS-EI m/z (relative intensity) 356 (M−$(CH_2)_2OH^+$, 1), 280 (M−$BnOCH_2^+$, 8), 247 (10), 246 (56), 155 (7), 140 (7), 125 (10), 124 (9), 108 (7), 92 (10), 91 (100), 65 (7); HRMS calcd for $C_{22}H_{28}NO_4S$ (M+H^+): 402.1739, found: 402.1745.

Relevant NOESY correlations (500 MHz, $CDCl_3$)



68

The absence of scalar coupling between H^1 and H^2 (J^3(H^1–H^2)≈0 Hz) confirmed the stereochemical assignment.[46]

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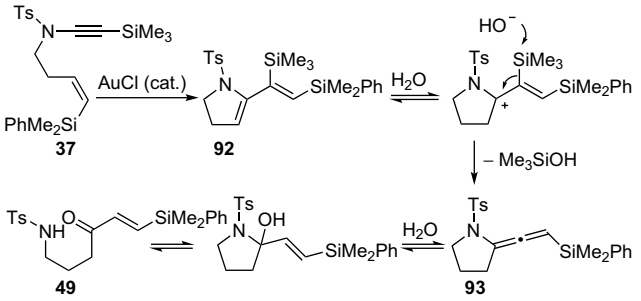

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