Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 3856–3871
Tetrahedron

Radical cascade cyclizations and platinum(II)-catalyzed cycloisomerizations of ynamides

Frédéric Marion, Julien Coulomb, Aurore Servais, Christine Courillon,* Louis Fensterbank* and Max Malacria*

Université Pierre et Marie Curie, Laboratoire de Chimie Organique, associé au CNRS, Institut de Chimie Moléculaire FR2769, 04 place Jussieu, Tour 44-54 2ème étage, B229, 75252 Paris Cedex 05, France

Received 14 November 2005; accepted 26 November 2005

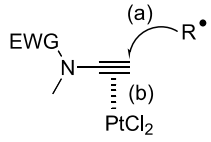
Available online 28 February 2006

Abstract—Ynamides are tested as new partners in radical and organometallic transformations. A radical cascade involving a 5-*exo-dig* cyclization followed by a 6-*endo-trig* radical trapping transforms ynamides into hetero-polycyclic compounds such as isoindoles, isoindolinones and pyrido-isoindolones. Various ene–tosylynamides react with platinum(II) chloride and lead to bicyclic nitrogenated heterocycles. This unprecedented and easily operated process can be coupled with a hydrolysis of the intermediate cyclic tosylenamides in a one-pot transformation, which provides cyclobutanones.

1. Introduction

As a coincidence, the pioneer works on ynamines were reviewed 30 years ago in our university by late Professor Jacqueline Ficini.[1] She, and other groups successfully prepared and studied a moiety bearing a very high organic synthetic potential, the triple bond, attached to a nitrogen atom whose both electron donating ability and natural abundance are seminal for chemical processes and target oriented strategies.[2–4] However, the reactivity of ynamines has not been developed until recently due to their high sensitivity towards hydrolysis and to their difficult preparation.[5] Interestingly, the substitution of the nitrogen atom with an electron withdrawing group helps stabilizing the yne–nitrogen association under the form of an ynamide, which reaches a compromise between reactivity and stability. The most frequently reported ynamides are sulfonamides, cyclic carbamates and lactams. Since the first preparation of ynamides by Viehe in 1972, numerous methods have been described in the literature.[6–21] Very recently copper-mediated *N*-alkynylations as synthetic preparations of ynamides were reported by Danheiser and Hsung to obtain carbamates, sulfonamides and lactams mainly.[22,23] The growing development of several efficient methods for the synthesis of ynamides is due to their original and very diverse reactivity and to the synthetic importance of these versatile building blocks. Indeed ynamides can undergo metal-catalyzed [2+2+2][24] and [2+2+1][14,15,25] cycloadditions, [2+2][12,26] and [4+2][12,27] cycloadditions, ring-closing metatheses,[28] addition reactions,[29] palladium-catalyzed cross-couplings,[30] electrocyclic processes[31] and carbometallation reactions.[32] Being deeply involved both in radical and organometallic mechanistical studies as well as synthetic processes, we examined ynamides as new partners in the two types of approaches.

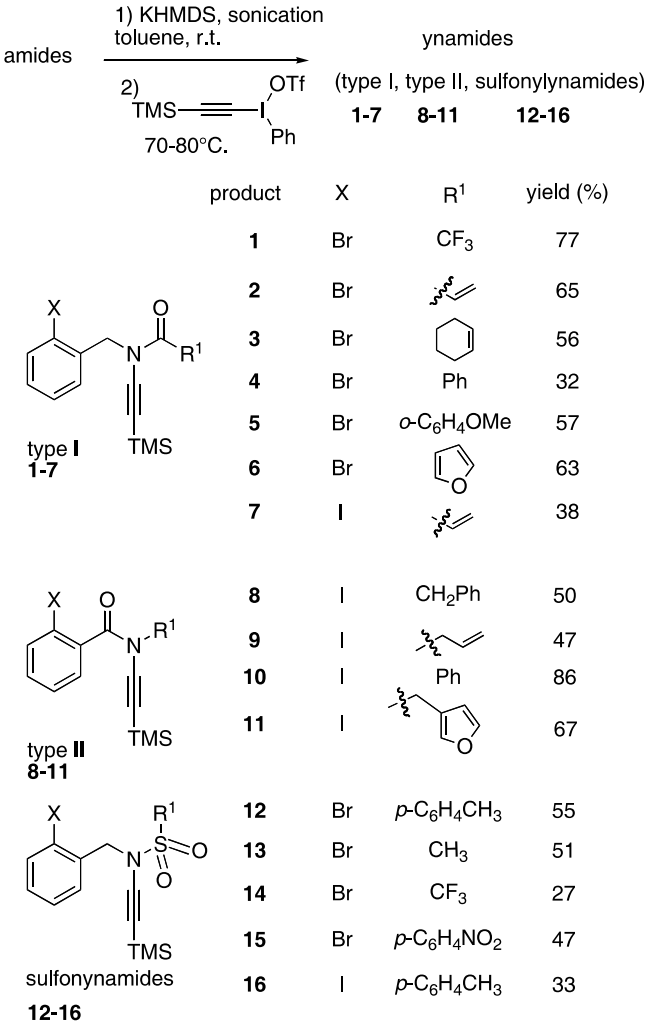
First, our interest in radical cyclization cascades[33] and in the discovery of new radical reaction partners[34] together with the emergence of radical chemistry in the field of heterocyclic synthesis[35] prompted us into the study of ynamides radical transformations (pathway (a) in scheme 1).[36] Second, we investigated the platinum(II) dichloride catalyzed cycloisomerization of ene–tosylynamides (pathway (b) in Scheme 1), targeting the promotion of charge controlled processes on the nitrogen substituted triple bond by $PtCl_2$.



Scheme 1.

Keywords: Cycloisomerization; Heterocycles; Platinum; Radical Cascades; Radical cyclization; (Tosyl)-ynamides.
* Corresponding authors. Tel.: +33 14427 5996; fax: +33 14427 7360 (C.C.); tel.: +33 14427 7068; fax: +33 14427 7360 (L.F.); tel.: +33 14427 3586; fax: +33 14427 7360 (M.M.); e-mail addresses: christine.courillon@upmc.fr; louis.fensterbank@upmc.fr; max.malacria@upmc.fr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.092



product	X	R^1	yield (%)
1	Br	CF_3	77
2	Br		65
3	Br		56
4	Br	Ph	32
5	Br	*o*-C_6H_4OMe	57
6	Br		63
7	I		38
8	I	CH_2Ph	50
9	I		47
10	I	Ph	86
11	I		67
12	Br	*p*-$C_6H_4CH_3$	55
13	Br	CH_3	51
14	Br	CF_3	27
15	Br	*p*-$C_6H_4NO_2$	47
16	I	*p*-$C_6H_4CH_3$	33

Scheme 2.

2. Radical cyclization cascades of ynamides

2.1. Synthesis of precursors

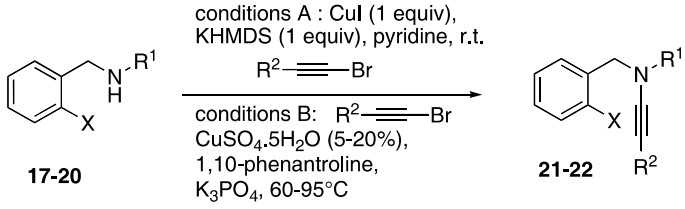
We report herein the first use of ynamides in radical cyclizations leading to polycyclic nitrogen heterocycles. Initially, the silylated carboxamides precursors **1**–**11** of type **I** and **II** were easily prepared according to Witulski's[14] method, which involves the Michael addition of an amide to an alkynyliodonium salt, whilst sulfonylynamides **12**–**16** were obtained in less satisfying yields (Scheme 2).

We have tested other preparation methods, especially following Hsung's and Danheiser's procedures.[22,23] For instance, coupling of 2-bromobenzyltosylamide **18** with phenylethynylbromide succeeds in a yield of 75 and 80%, respectively, in the presence of copper(I) iodide in pyridine and with copper (II) sulfate and 1,10-phenantroline. This result is comparable with the transformation of benzyltosylamide **17** reported in the literature.[22,23,37] When we submitted conjugated carboxamides such as **19** or **20** to the same set of experimental conditions, we could only recover the starting material. (Scheme 3) This lack of reactivity may be due to the deactivation of the copper catalyst by the amide as reported by Riddell[26] and Buchwald.[38]

Therefore, we rather prepared the carboxamides precursors **1**–**11** by reacting them as depicted in scheme 2, whilst further desilylation[14] and subsequent alkylation[17a] of compounds **2**, **3**, **7** and **9** gave an easy access to various substituted ynamides **23**–**28** (Scheme 4).

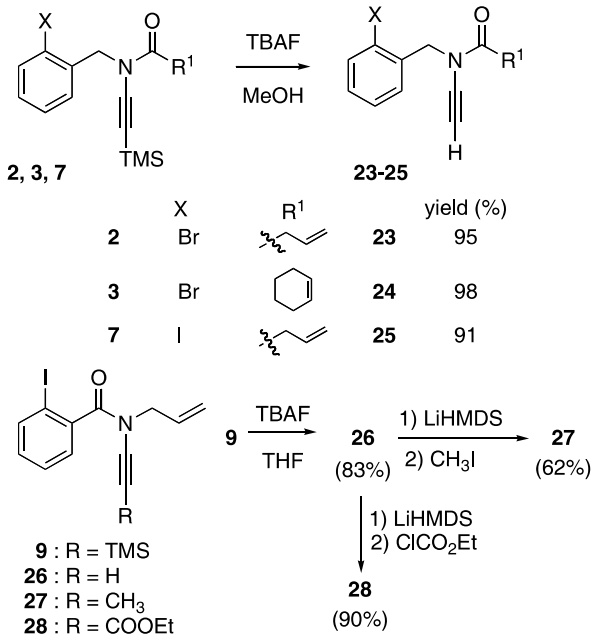
2.2. Radical cyclization

We first examined the 5-*exo-dig* cyclization with differently protected ynamides (sulfonylynamides **12**–**17**, type **I**



substrate	R^1	X	R^2	conditions	yield (%)
17	Ts	H	Ph	A	78
17	Ts	H	Ph	B	96
18	Ts	Br	Ph	A	75
18	Ts	Br	Ph	B	80
19		H	Ph	A or B	0
20		Br	Ph or TMS	A or B	0

Scheme 3.

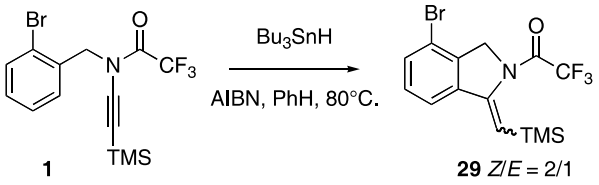


Scheme 4.

compounds **1**–**7** and type **II** compounds **7**–**11**) obtained either from the corresponding amides (Scheme 1) or by desilylation of the triple bond and further substitution if necessary (Scheme 4).

Since radical cyclization of various sulfonamides has been well studied in the literature,[35] in our first attempts we submitted sulfonylynamides **12**–**17** to tributyltin hydride/AIBN initiation conditions in benzene. Cyclization failed and the results could not be improved upon changing the halogen atom or the electronic properties of the sulfonyl group. These precursors reacted slowly and sluggishly to give only trace amounts of the 5-*exo-dig* products in the case of the methanesulfonyl- and the trifluoromethanesulfonyl-protected ynamides. The outbreak of a deep purple colour in the reaction mixture leads us in speculating about the formation of a persistent radical, which would not allow the cascade process to evolve and proceed.

Next, we turned our attention to the trifluoroacetamide **1**, which cyclized in refluxing benzene in the presence of tin hydride and AIBN in 78% yield to give the isoindole **29** as a mixture of two diastereomers on the double bond in a 2/1 ratio (Scheme 5). NOE experiments have shown that the *Z* diastereomer was the main compound, suggesting that the reduction of the vinylic radical was governed by its stability and therefore by allylic strain.



Scheme 5.

With this preliminary result in hands, we next assumed that the intermediate vinylic radical could be trapped by another insaturation. Gratifyingly, we could assist to the radical cyclization cascade with good yields when reacting type **I** precursors, which contain an activated double bond (Table 1).

In the case of bromobenzyl precursors (entries 1–3 and 6–9), the cyclization products could be observed only with silylated ynamides (entries 1, 2 and 6–8). Slow addition of tin hydride was necessary to obtain the cascade products in good yields (entries 2 and 7).

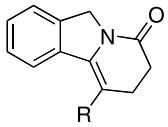
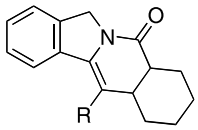
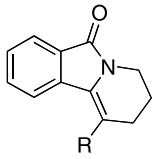
For iodobenzyl compounds, the cyclization products were obtained in good yields without slow addition and in the case of silylated and monosubstituted triple bonds (Table 1, entries 4 and 5). This suggests that the addition of the tributylstannyl radical[39] to the triple bond is competitive with the bromine atom abstraction and is the major pathway when the ynamide is monosubstituted. The use of tristrimethylsilylsilane[40] as the reductor in order to try to avoid this side reaction did not allow us to isolate any cyclization product in the case of the cyclohexenyl precursor (entries 8 and 9). The observed products were issued from a radical cascade, which involves a 5-*exo-dig* cyclization followed by radical trapping in a 6-*endo-trig* mode for an activated terminal or endocyclic double bond. This cascade shows an excellent regioselectivity in the case of type **I** precursors, which contain activated acceptors.

The same 5-*exo-dig*/6-*endo-trig* regioselectivity was observed when reacting type **II** compounds with non-activated acceptors (Table 1). The substitution on the triple bond was studied on type **II** compounds. In order to avoid the addition of tin on the triple bond, we have also chosen an iodo-precursor. We obtained good yields for mono- and di-substituted ynamides.(Table 1) The yield decreased when the triple bond was activated with an ester group. The addition of tin became then possible and the yield could not be improved with slow addition of the hydride.

In the case of ynamides **4**, **5**, **8** and **10**, an aromatic acceptor is either conjugated with the amide or linked to it through a methylene group (Table 2). We observed that type **I** precursors **4** and **5** react differently than type **II** compounds **8** and **10**. When compound **4** reacts with tributyltinhydride, azabisisobutyronitrile in benzene at 80 °C, the aromatized tetracyclic product **37** is isolated after 2 h in 67% yield (entry 1). The formation of compound **37** under reducing conditions and the absence of traces of the reduced vinylsilane indicate that the cascade process is faster than the reduction of the intermediate vinyl radical. This could also be observed for the methoxysubstituted ynamide **5**, which cyclizes slightly less rapidly for 16 h and gives compound **38** in a lower yield of 54% (entry 2). No product issued from an *ipso* cyclization followed by a rearrangement was isolated.[35d,41]

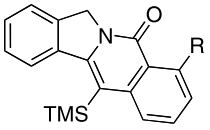
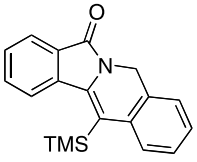
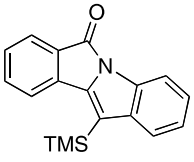
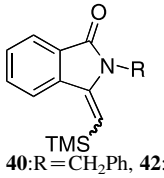
Reaction (under the same classical radical conditions mentionned above) of type **II** ynamide **8** gives a 1/1 mixture of the two diastereomeric forms of compound **40** in a yield of 57% whilst traces of the tetracyclic compound **39** could be identified in the crude material (entry 3). Compound **10** was transformed into a mixture of the tetracyclic isoindolinone **41** (23%) and the two

Table 1

	Entry	Ynamide	R	Yield (%)[a]		Product
Type **I**	1	**2**	TMS	42	**30**	
	2	**2**	TMS	70[b]	**30**	
	3	**23**	H	0[b]		
	4	**7**	TMS	83	**30**	
	5	**25**	H	54	**31**	
	6	**3**	TMS	45	**32**	
	7	**3**	TMS	75[b]	**32**	
	8	**3**	TMS	54[c]	**32**	
	9	**24**	H	0,[b] 0[c]		
Type **II**	10	**9**	TMS	90	**33**	
	11	**26**	H	78	**34**	
	12	**27**	CH_3	84	**35**	
	13	**28**	CO_2Et	45	**36**	

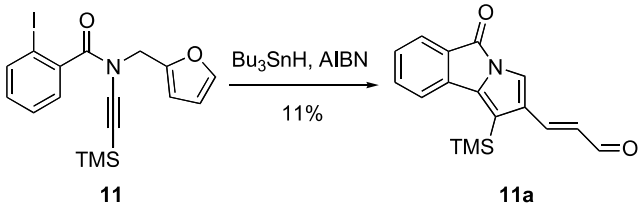
[a] A benzene solution (15 mL) of ynamide (0.25 mmol), tin hydride (2 equiv) and AIBN (0.5 equiv) was refluxed until the starting material disappeared.
[b] Slow addition of the hydride was performed.
[c] Tristrimethylsilylsilane was used as reductor.

Table 2

	Entry	Ynamide	Yield (%)[a]	Product
Type **I**	1	**4**	67	**37**
	2	**5**	54	**38**
	3	**8**	57	**40** (*Z*/*E*:1/1)
Type **II**	4	**10**	94	**41** (23%)+**42** (71%) (*Z*/*E*: 2:1)
	5	**8**	46[a]	**39**
	6	**10**	62[a]	**41**
	 **37**:R=H, **38**:R=OMe	 **39**	 **41**	 **40**:R=CH_2Ph, **42**:R=Ph

[a] Photolysis of hexabutylditin in toluene is used in the reaction.

diastereomers (*Z*/*E*: 2:1) of compound **42** (71%) (entry 4). Slow addition of tributyltin hydride (0.25 mmol h^{-1}) neither increased the formation of compound **39** nor significantly modified the ratio of compounds **41** and **42**. When we carried out the reaction under atom transfer conditions (photochemical homolytic cleavage of hexabutylditin in toluene) in order to try to avoid the intermediate reduction products, the type **II** precursors gave only the tetracyclic products **39** and **41**, respectively, in a yield of 46 (40 h) and 62% (7 h) (entries 5 and 6). The difference in behaviour between type **I** and type **II** ynamides bearing an aromatic moiety, which plays the role of trapping the intermediate vinyl radical speaks for the importance of the place of the amide function. When the ynamide bears an heteroaromatic ring as the acceptor moiety such as a furanyl substituent the reaction developed differently in the case of type **I** and **II** compounds. We failed in initiating the radical transformation of compound **6** whilst compound **11** was transformed into a compound that we could identify as the highly conjugated aldehyde **11a** probably via an *ipso*[42] cyclisation and an oxidative fragmentation process.(Scheme 6)



11 **11a**

Scheme 6.

We have demonstrated that ynamides are excellent partners for radical chemistry. We have described a new radical cyclization cascade process, which leads to isoindole, isoindolinones and pyrido-isoindolones in good yields. These results bring new perspectives for the development of ynamides and the application of their reactivity in the field of heterocyclic chemistry.

3. Platinum(II) chloride catalyzed cycloisomerization of ynamides

The transition metal catalyzed cycloisomerization of enyne systems is a powerful synthetic tool that has witnessed intense development.[43] Nevertheless, there is still room for the implementation of new partners in this process. Among all potential candidates, ene–tosylynamides are highly appealing substrates. Because of the presence of the nitrogen atom directly attached to the triple bond, one can anticipate charge controlled processes.[5,24a,31b] This led us to the use of platinum(II) dichloride as catalyst, since this versatile reagent is known to promote charge build-up on enyne systems.[44,45] In addition, the resulting products should incorporate valuable nitrogen heterocycles. This has also been demonstrated by Hsung with the development of a $PtCl_2$-catalyzed keteniminium Pictet–Spengler cyclization.[46] Herein, we describe our results of a versatile organometallic process, which transforms different ene–tosylynamides, in the presence of $PtCl_2$, into bicyclic nitrogenated heterocycles.

3.1. Synthesis of precursors

The precursors we have used in this part were prepared following the Brückner's alternative transformation of formamides.[7] After a Mitsonobu transformation, the alkylated tosylamines are formylated with Katritsky's reagent: *N*-formylbenzotriazole.[47] Dichloroolefination and a butyllithium-triggered Fritsch–Buttenberg–Wiechell rearrangement sets the alkyne function. This procedure allowed us to obtain various ene–tosylynamides, which are utilized in this work as precursors of original $PtCl_2$-catalyzed cycloisomerizations (Scheme 7).

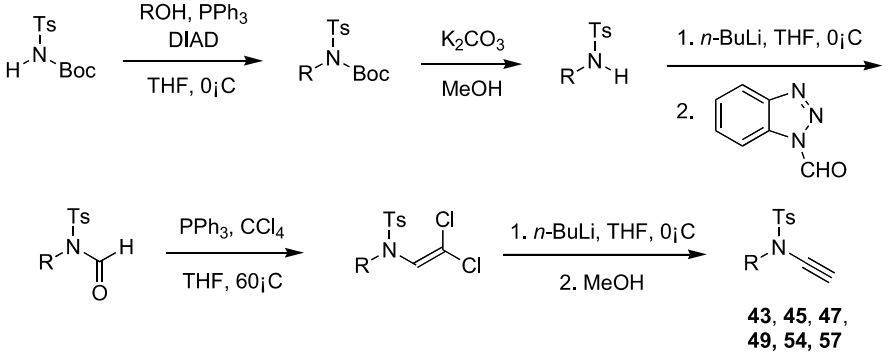
3.2. Cycloisomerizations

Our first attempt consisted in exposing ene–ynamide **43** to $PtCl_2$ (5 mol%) in toluene at 80 °C and led to the metathesis product **44** in 98% yield, whose structure was secured by comparing to Mori's data. (Scheme 8). Mori has indeed investigated the ring-closing metathesis transformation of **43** and found out that this reaction was accelerated in the presence of the second generation Grubb's catalyst.[28b] Moreover, she performed efficient ring-closing metathesis with several precursors bearing a different carbon tether between the amide function and the carbon–carbon double bond like precursors **45** and **47**. We show here a completely distinct and original reactivity of these substrates in the presence of platinum dichloride. Thus, in the case of ene–tosylynamide **45**, cyclization occurred and yielded the bicyclic[4.2.0] compound **46**.[48] This fragile structure, partially degrading during the purification process, was obtained in 34% yield, which we had some difficulty to reproduce since these reactions proved to be sensitive to moisture. The bicyclic derivative **48** was similarly obtained by reacting the β-dimethyl-substituted ene–ynamide **47** with 5 mol equiv of $PtCl_2$ in 71% yield. The structural assignment for **46** and **48** was based on the following data: ^1H NMR spectra show no stereogenic centre and ^{13}C NMR spectra display no CH signal, indicating that the double bond is shared by the two cycles. Quaternary carbon signals around 122 and 135 ppm confirm the structure of the bicyclic product. These platinum(II)-catalyzed cyclizations could not easily be monitored by TLC because of close R_f for the product and the starting material which, in addition, reveal as faint spots. Therefore, we followed the consumption of the ene–ynamide by IR spectroscopy and checked the vanishing of the triple bond band.

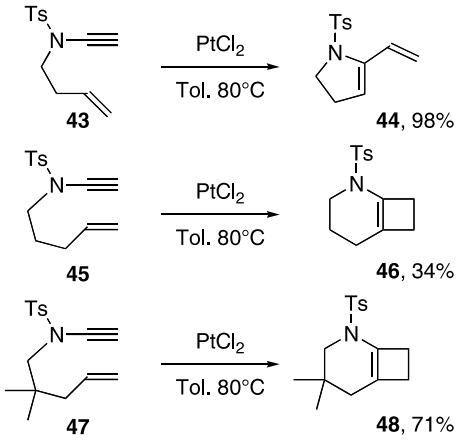
Because of the general lability of the final products,[49] we decided to transform the crude bicyclic products directly into more stable compounds through a second reaction in a one-pot process.

First, we performed ozonolysis, which provided easily isolated keto-lactams **50–52**, that could be useful building blocks in total synthesis of more complex alkaloid natural products. Nevertheless, the moderate yields (Table 3), yet consistent with literature,[50] drove us to switch to a hydrolysis reaction as the second step. Thus, after cycloisomerization reaction in presence of 10 mol% of $PtCl_2$, addition of a 1 M HCl solution to the crude cycloisomerized product gave cyclobutanones formed by hydrolysis of the intermediate enamines. The results of this cyclization–hydrolysis sequence are summarized in Table 3.

The four atom-tethered substrates **45** and **47** are transformed in good yields into the corresponding cyclobutanones **53**, **56**. Alkyl substitution is tolerated both on the alkyne partner (precursor **59**) and on the alkene one (precursors **54** and **57**). In the case of **57**, the non-opened bicyclic aminal **58**, presumably cis[51] was obtained in 76% yield. As anticipated,



Scheme 7.



Scheme 8.

Table 3

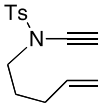
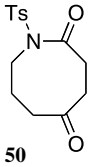
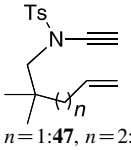
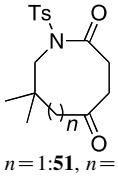
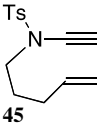
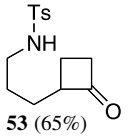
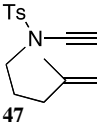
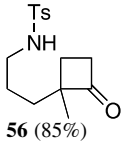
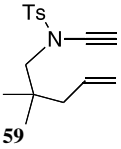
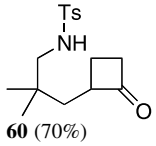
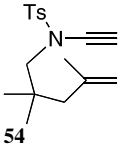
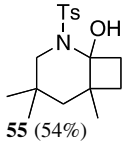
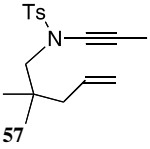
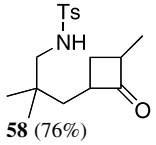
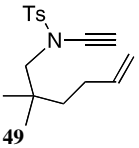
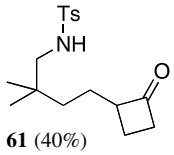
Ynamides	Keto-lactams	Yield (%)
 **45**	 **50**	20
 $n=1$:**47**, $n=2$:**49**	 $n=1$:**51**, $n=2$:**52**	37,24

Table 4

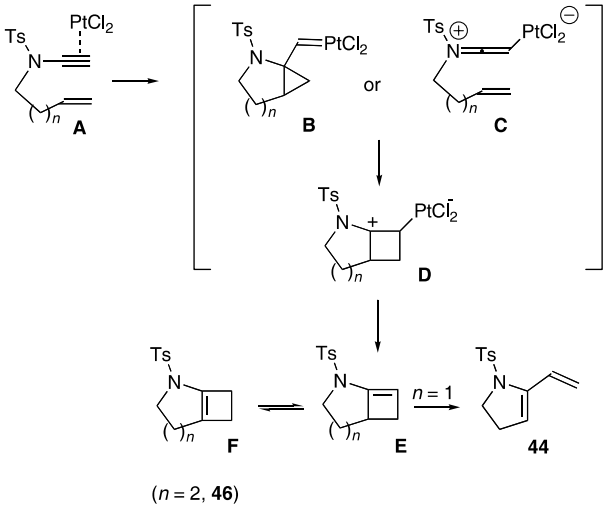
Ynamides	Cyclobutanones
 **45**	 **53** (65%)
 **47**	 **56** (85%)
 **59**	 **60** (70%)
 **54**	 **55** (54%)
 **57**	 **58** (76%)
 **49**	 **61** (40%)

introduction of a *gem*-dimethyl group in the tether resulted in improved yields (substrate **45** and **47** vs **54** and **57**).[52]

Lengthening the tether up to five atoms, corresponding to an intermediate [5,2,0]-bicyclic adduct still gave a satisfactory yield of cyclobutanone **61**. In this case, some aminal could also be observed in the crude product but was not isolated after separation on silica gel (Table 4).

3.3. Mechanism

The original results summarized in Scheme 8 and in both Tables 3 and 4 show two types of products whose formation would be dependent from the tether length. For $n=1$, which corresponds to a 1,6-enyne precursor, the formal metathesis diene (**44**) is isolated; for $n=2$, bicyclo[$n+2.0.2$] products are obtained. Although the formation of 1,3-dienes does not necessarily transit via a cyclobutene,[53] the proposition of a common reaction pathway involving bicyclic intermediate **E** with two distinct evolutions appears appropriate. Ring strain associated with the cyclobutene moiety would direct the fate of this intermediate. Presumably, for $n=1$, the severe ring strain would promote the electrocyclic ring opening of **E** to provide the diene **44**. With a six-membered ring fused to the cyclobutene, the strain is reduced and isomerization of the double bond from *exo* to *endo* at the ring junction would be favourable, giving products **F**. This is supported by the isolation of **46** and **48**. However, in the case of precursors **54** and **57**, intermediate **F** is not attainable. Instead, intermediate of type **E**[54] could also lead to the hydrolysis products **55** and **58** (Scheme 9).



Scheme 9.

Several mechanistic scenarios are possible for the generation of key intermediate **E**. All begin with the electrophilic activation of the yne partner by the π-Lewis acid (complex **A**). Then, as supported by DFT calculations of Soriano,[51] and consitent with Echavarren modelizations,[55] evolution of a cyclopropylplatina carbene intermediate **B** could lead to **D**. Alternatively, a ketenimium intermediate **C**, as proposed by Hsung[46] would undergo a [2+2] cycloaddition and ensure the construction of the cyclobutyl ring. Both pathways could transit via stabilized carbocation **D** to provide **E**. 'Homoallyl-cyclopropylmethyl-cyclobutyl' cation **D** could also originate from Fürstner's cationic manifold proposal.[44d]

4. Conclusion

We herein report the first use of ene–ynamides as versatile partners for radical cyclizations and $PtCl_2$-catalyzed cycloisomerization reactions. Efficient and original new accesses to nitrogenated polycyclic derivatives have been worked out. The radical approach implies two main classes of ynamides, which were designed to be precursors to an aryl radical that is suitably placed for cyclization onto the ynamide. On type **I** and **II** *N*-alkynylcarboxamides, 5-*exo* cyclization was easily and efficiently carried out, and examples of tandem 5-*exo*, 6-*endo*-cyclizations have led to nitrogen-containing heterocyclic compounds. The key factors that affected the success of these reactions were shown to be the starting halide, and the degree of substitution of the alkyne. The extension of this cascade process to substrates in which the final cyclization would occur onto an aryl or an heteroaryl ring completes this study and opens it towards future synthetic developments in the field of medicinal chemistry. In the case of the Pt(II) chemistry,[56] a formal [2+2] cycloaddition gives birth to versatile cyclobutenyl bicyclic substrates that we could ozonolyse to provide medium-sized nitrogen heterocycles, and hydrolyze to give various cyclobutanone derivatives. In the latter case, the reaction corresponds to an intramolecular addition of a ketene on the alkene partner via a nitrogen tether. These preliminary elements of reactivity confirm the high synthetic potential of the introduction of ene–ynamides in organometallic chemistry and pave the way for important applications we will disclose in due course.

5. Experimental

^1H and ^{13}C NMR spectra were recorded at rt at 400 and 100 MHz, respectively, on an ARX 400 Bruker spectrometer. Chemical shifts are reported in parts per million referenced to the residual proton resonances of the solvents. Coupling constants are expressed in Hertz. We use (I), (II), (III) and (IV) to caracterize primary, secondary, tertiary and quaternary carbons.

Infrared (IR) spectra were recorded with a Bruker tensor 27 (ATR diamond spectrometer). Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F 254. Silica gel Merck Geduran SI (40–63 μm) was used for column chromatography using Still's method.

All melting points are uncorrected. THF and Et_2O are distilled from sodium benzophenone ketyl, CH_2Cl_2, pentane and toluene are distilled, respectively, from CaH_2 and Na/K.

5.1. General procedure for the formation of ynamides

To a solution of amide (2 mmol) in toluene (60 mL) was added at ambient temperature KHMDS (powder, 2.2 mmol), the resulting mixture was sonicated for 30–60 min. The reaction medium was then heated to 70–80 °C and the iodonium salt (2.5 mmol) was added under vigorous stirring. After 30 min the temperature was raised to rt and silica (10 g) was added. The solvent was then removed under reduced pressure and chromatography on silica gel (9:1 petroleum ether/ethyl acetate) of the crude residue afforded ynamides.

5.1.1. *N*-(2-Bromo-benzyl)-2,2,2-trifluoro-*N*-trimethylsilanylethynyl-acetamide 1. Yield=77%. Clear oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.62 (d, J=7.6 Hz, 1H), 7.36–7.23 (m, 3H), 4.91 (s, 2H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 158.3 (q, 1C, IV, J=36.4 Hz), 133.2 (III), 132.99 (IV), 130.9 (III), 130.22 (III), 127.7 (III), 124.46 (IV), 117.1–114.2 (q, 1C, IV, J=287.2 Hz), 90.9 (IV), 78.0 (IV), 53.30 (II), −0.4 (3C, I); ^{19}F NMR ($CDCl_3$, 376 MHz): −71.5; IR (neat) cm^{-1}: 3064, 2187, 1725, 1251, 1154.

5.1.2. *N*-(2-Bromo-benzyl)-*N*-trimethylsilanylethynyl-acrylamide 2. Yield=65%. Pale yellow solid; mp 40–43 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.58 (d, J=8.0 Hz, 1H), 7.31 (m, 2H), 7.17 (t, J=8.0 Hz, 1H), 7.14 (dd, J=16.8, 10.2 Hz, 1H), 6.54 (dd, J=16.8, 1.6 Hz, 1H), 5.88 (dd, J=10.2, 1.6 Hz, 1H), 4.89 (s, 2H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.3 (IV), 134.7 (IV), 132.8 (III), 131.3 (II), 130.3 (III), 129.4 (III), 127.5 (III), 126.5 (III), 124.1 (IV), 95.6 (IV), 76.5 (IV), 51.3 (II), −0.1 (3C, I); IR (neat) cm^{-1}: 3065, 3032, 2173, 1685, 1625, 1244. Anal. Calcd for $C_{15}H_{18}BrNOSi$ (336.29): C, 53.57; H, 5.39; N, 4.16. Found: C, 53.42; H, 5.45; N, 4.08.

5.1.3. Cyclohex-1-enecarboxylic acid (2-bromo-benzyl)-trimethylsilanylethynyl-amide 3. Yield=56%. Pale yellow solid; mp 37–39 °C; ^1H NMR ($CDCl_3$, 200 MHz): 7.55 (d, J=7.4 Hz, 1H), 7.28 (m, 3H), 7.15 (m, 1H), 6.52 (h, J=2.0 Hz, 1H), 4.79 (s, 2H), 2.34 (m, 2H), 2.14 (m, 2H), 1.64 (m, 4H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 172.2 (IV), 135.2 (IV), 134.7 (III), 132.9 (III), 132.6 (IV), 130.3 (III), 129.3 (III), 127.4 (III), 124.1 (IV), 97.6 (IV), 74.7 (IV), 52.0 (II), 25.3 (II), 25.0 (II), 22.0 (II), 21.6 (II), 0.1 (3C, I); IR (neat) cm^{-1}: 3064, 3032, 2164, 1679, 1278. Anal. Calcd for $C_{19}H_{24}BrNOSi$ (390.38): C, 58.46; H, 6.20; N, 3.53. Found: C, 58.47; H, 6.08; N, 3.53.

5.1.4. *N*-(2-Bromo-benzyl)-*N*-trimethylsilanylethynyl-benzamide 4. Yield=32%. Pale yellow solid; mp 51–53 °C; ^1H NMR (C_6D_6, 400 MHz): 8.04 (dd, J=6.6, 2.0 Hz, 2H), 7.39 (td, J=8.1, 1.5 Hz, 2H), 7.15 (m, 3H), 6.98 (td, J=7.6, 1.5 Hz, 1H), 6.75 (td, J=8.1, 2.0 Hz, 1H), 5.03 (s, 2H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.7 (IV), 135.1 (IV), 133.2 (IV), 133.0 (III), 131.7 (III), 130.6 (III), 129.6 (III), 129.1 (2C, III), 127.4 (2C, III), 127.5 (III), 124.3 (IV), 97.4 (IV), 75.9 (IV), 52.6 (II), −0.2 (3C, I); IR (neat) cm^{-1}: 3086, 3067, 3029, 3006, 2171, 1673, 1286.

Anal. Calcd for $C_{19}H_{20}BrNOSi$ (386.36): C, 59.07; H, 5.22; N, 3.63. Found: C, 59.15; H, 5.21; N, 3.52.

5.1.5. *N*-(2-Bromo-benzyl)-2-methoxy-*N*-trimethylsilanylethynyl-benzamide 5. Yield=57%. Pale yellow solid; mp 96–98 °C; ^{1}H NMR (C_6D_6, 200 MHz): 7.65 (dd, J=7.6, 1.3 Hz, 1H), 7.50 (dd, J=7.6, 1.3 Hz, 1H), 7.42 (d, J=7.6 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.08 (td, J=7.5, 1.1 Hz, 1H), 6.80 (m, 2H), 6.56 (d, J=8.2 Hz, 1H), 5.14 (s, 2H), 3.45 (s, 3H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): 170.8 (IV), 156.6 (IV), 135.1 (IV), 132.9 (III), 131.6 (III), 129.6 (III), 129.3 (III), 128.5 (III), 127.6 (III), 124.7 (IV), 123.7 (IV), 120.5 (III), 110.9 (III), 97.1 (IV), 74.27 (IV), 55.8 (I), 51.6 (II), 0.00 (3C, I); IR (neat) cm^{-1}: 3065, 3029, 3009, 2178, 1681, 1273. Anal. Calcd for $C_{20}H_{22}BrNO_2Si$ (416.38): C, 57.69; H, 5.33; N, 3.36. Found: C, 57.71; H, 5.37; N, 3.53.

5.1.6. Furan-2-carboxylic acid (2-bromo-benzyl)-trimethylsilanylethynyl-amide 6. Yield=63%. Pale yellow solid; mp 113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.66 (d, 1H, J=3.5 Hz), 7.64 (d, J=1.0 Hz, 1H), 7.60 (d, J=8.1 Hz, 1H), 7.38 (dd, J=7.6, 1.5 Hz, 1H), 7.31 (t, J=7.6 Hz, 1H), 7.20 (td, J=1.5, 7.1 Hz, 1H), 6.54 (dd, J=3.5, 1.5 Hz, 1H), 5.01 (s, 2H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 158.6 (IV), 146.1 (III), 145.3 (IV), 134.7 (IV), 132.9 (III), 132.8 (IV), 130.6 (III), 128.5 (III), 127.5 (III), 124.3 (IV), 119.1 (III), 111.5 (III), 96.8 (IV), 76.7 (IV), 52.6 (II), −0.1 (3C, I); IR (neat) cm^{-1}: 2958, 2164, 1662, 1465, 1294, 839, 744. Elemental Anal. Calcd for $C_{17}H_{18}BrNO_2Si$ (376.32): C, 54.26; H, 4.82; N, 3.72. Found: C, 54.16; H, 4.90; N, 3.64.

5.1.7. *N*-(2-Iodo-benzyl)-*N*-trimethylsilanylethynyl-acrylamide 7. Yield=38%. Pale yellow solid; mp 34–36 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.86 (dd, J=7.8, 1.0 Hz, 1H), 7.32 (m, 2H), 7.11 (dd, J=16.9, 10.4 Hz, 1H), 7.00 (td, J=7.8, 1.9 Hz, 1H), 6.55 (dd, J=16.9, 1.9 Hz, 1H), 5.89 (dd, J=10.4, 1.9 Hz, 1H), 4.83 (s, 2H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.4 (IV), 139.5 (III), 137.8 (IV), 131.3 (II), 129.6 (III), 129.5 (III), 128.3 (III), 126.5 (III), 99.4 (IV), 95.5 (IV), 76.7 (IV), 55.7 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 3058, 2172, 1685, 1236. Anal. Calcd for $C_{15}H_{18}INOSi$ (383.29): C, 47.00; H, 4.73; N, 3.65. Found: C, 47.14; H, 4.78; N, 3.58.

5.1.8. *N*-Benzyl-2-iodo-*N*-trimethylsilanylethynyl-benzamide 8. Yield=50%. Pale yellow solid; mp 46–48 °C; ^{1}H NMR (C_6D_6, 400 MHz): 7.58 (m, 3H), 7.25 (m, 2H), 7.18 (m, 1H), 7.08 (dd, J=7.5, 1.6 Hz, 1H), 6.88 (td, J=7.5, 1.0 Hz, 1H), 6.57 (td, J=7.8, 1.6 Hz, 1H), 4.83 (s, 2H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.2 (IV), 141.3 (IV), 138.8 (III), 135.3 (IV), 130.7 (III), 129.2 (2C, III), 128.4 (2C, III), 128.1 (III), 127.8 (III), 127.7 (III), 96.3 (IV), 92.2 (IV), 79.2 (IV), 51.6 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 3066, 3023, 2170, 1686, 1297, Anal. Calcd for $C_{19}H_{20}INOSi$ (433.36): C, 52.66; H, 4.65; N, 3.23. Found: C, 52.40; H, 4.87; N, 3.18.

5.1.9. *N*-Allyl-2-iodo-*N*-trimethylsilanylethynyl-benzamide 9. Yield=47%. Pale yellow solid; mp 36–38 °C; ^{1}H NMR (C_6D_6, 400 MHz): 7.59 (d, J=7.5 Hz, 1H), 7.13 (dd, J=7.5, 1.5 Hz, 1H), 6.91 (t, J=7.5 Hz, 1H), 6.60 (t, J=7.5 Hz, 1H), 6.01 (m, 1H), 5.34 (dd, J=17.1, 1.2 Hz, 1H), 5.19 (dd, J=10.3, 1.0 Hz, 1H), 4.28 (d, J=6.0 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.2 (IV), 141.4 (IV), 138.8 (III), 130.8 (III), 130.7 (III), 127.7 (III), 127.7 (III), 119.4 (II), 96.1 (IV), 92.2 (IV), 75.6 (IV), 50.2 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 3085, 3053, 3021, 2170, 1685, 1644, 1291. Anal. Calcd for $C_{15}H_{18}INOSi$ (383.29): C, 47.00; H, 4.73; N, 3.65. Found: C, 47.08; H, 4.65; N, 3.62.

5.1.10. 2-Iodo-*N*-phenyl-*N*-trimethylsilanylethynyl-benzamide 10. Yield=86%. Pale yellow solid; mp 86–88 °C; ^{1}H NMR (C_6D_6, 400 MHz): 7.89 (d, J=7.5 Hz, 2H), 7.59 (dd, J=8.0, 1.0 Hz, 1H), 7.21 (m, 2H), 7.15 (dd, J=7.5, 1.5 Hz, 1H), 7.05 (t, J=7.5 Hz, 1H), 6.92 (td, J=7.5, 1.0 Hz, 1H), 6.62 (td, J=7.8, 1.5 Hz, 1H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.0 (IV), 141.5 (IV), 138.8 (III), 138.2 (IV), 130.9 (III), 129.2 (2C, III), 127.9 (III), 127.9 (III), 127.7 (III), 124.8 (III), 95.9 (IV), 92.4 (IV), 75.5 (IV), −0.2 (3C, I); IR (neat) cm^{-1}: 3075, 3058, 3028, 2172, 1697, 1301. Anal. Calcd for $C_{18}H_{18}INOSi$ (419.33): C, 51.56; H, 4.33; N, 3.34. Found: C, 51.54; H, 4.14; N, 3.27.

5.1.11. *N*-Furan-2-ylmethyl-2-iodo-*N*-trimethylsilanylethynyl-benzamide 11. Yield=67%. ^{1}H NMR (C_6D_6, 400 MHz): 7.58 (d, 1H, J=7.6 Hz, 1H), 7.15 (d, J=1.0 Hz, 1H), 7.08 (dd, J=7.6, 2.0 Hz, 1H), 6.87 (dt, J=7.6, 1.0 Hz, 1H), 6.57 (dt, J=7.6, 2.0 Hz, 1H), 6.42 (d, J=3.0 Hz, 1H), 6.13 (dd, J=3.0, 2.0 Hz, 1H), 4.81 (s, 2H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.0 (IV), 148.6 (IV), 142.7 (III), 141.0 (IV), 138.8 (III), 130.8 (III), 127.8 (III), 127.7 (III), 110.5 (III), 110.2 (III), 95.7 (IV), 92.1 (IV), 76.2 (IV), 44.2 (II), −0.3 (3C, I); IR (neat) cm^{-1}: 2171, 1685.

5.1.12. 3-(5-Oxo-1-trimethylsilanyl-5*H*-pyrrolo[2,1-*a*]-isoindol-2-yl)-propenal 11a. Yield=11%. ^{1}H NMR (C_6D_6, 400 MHz): 9.60 (d, J=7.6 Hz, 1H), 7.52 (d, J=7.6 Hz, 1H), 7.24 (m, 1H), 7.19 (d, J=15.7 Hz, 1H), 6.99 (s, 1H), 6.97 (t, J=7.6 Hz, 1H), 6.73 (t, J=7.6 Hz, 1H), 6.35 (dd, J=7.6, 15.7 Hz, 1H), 0.32 (s, 9H).

5.1.13. *N*-(2-Bromo-benzyl)-4-methyl-*N*-trimethylsilanylethynyl-benzenesulfonamide 12. Yield=55%. Pale yellow solid; mp 70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.85 (d, J=8.6 Hz, 2H), 7.55 (dd, J=8.1, 1.0 Hz, 1H), 7.43 (dd, J=7.6, 1.0 Hz, 1H), 7.38 (d, J=8.1 Hz, 2H), 7.31 (dd, J=8.6, 1.0 Hz, 1H), 7.18 (dt, J=7.6, 1.0 Hz, 1H), 4.59 (s, 2H), 2.44 (s, 3H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.9 (IV), 134.2 (IV), 133.8 (IV), 132.8 (III), 130.5 (III), 129.7 (2C, III), 127.9 (3C, III), 127.5 (III), 123.7 (IV), 95.0 (IV), 73.8 (IV), 55.0 (II), 21.7 (I), 0.0 (3C, I); IR (neat) cm^{-1}: 2956, 2160, 1679, 1594, 1442, 1368, 1248. Elemental Anal. Calcd for $C_{19}H_{22}BrNO_2SSi$ (436.44): C, 52.29; H, 5.08; N, 3.21. Found: C, 52.42; H, 5.26; N, 3.11.

5.1.14. *N*-(2-Bromo-benzyl)-*N*-trimethylsilanylethynyl-methanesulfonamide 13. Yield=51%. Pale yellow solid; mp 63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.61 (d, J=7.6 Hz, 1H), 7.52 (d, J=7.6 Hz, 1H), 7.37 (t, J=7.6 Hz, 1H), 7.23 (td, J=8.1, 1.5 Hz, 1H), 4.77 (s, 2H), 3.17 (s, 3H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 133.9 (IV), 133.0 (III), 132.2 (IV), 130.9 (III), 130.0 (III), 127.7 (III), 124.0 (IV),

94.0 (IV), 74.6 (IV), 54.8 (II), 38.7 (I), 0.0 (3C, I); IR (neat) cm^{-1}: 2950, 2161, 1600, 1353, 1166, 952.

5.1.15. *N*-(2-Bromo-benzyl)-C,C,C-trifluoro-*N*-trimethylsilanylethynyl-methanesulfonamide 14. Yield=27%. ^1H NMR ($CDCl_3$, 400 MHz): 7.30–7.20 (m, 2H), 6.90 (td, $J=7.5$, 1.2 Hz, 1H), 6.73 (td, $J=7.8$, 1.6 Hz, 1H), 4.65 (s, 2H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 133.5 (III), 132.6 (IV), 131.3 (III), 130.9 (III), 128.2 (III), 124.7 (IV), 120.0 (q, $J=322.6$ Hz, IV), 90.1 (IV), 75.6 (IV), 57.0 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 2900, 2180, 1411, 1228, 1198, 1134, 841.

5.1.16. *N*-(2-Bromo-benzyl)-4-nitro-*N*-trimethylsilanylethynyl-benzenesulfonamide 15. Yield=47%. ^1H NMR ($CDCl_3$, 400 MHz): 7.70–7.0 (m, 4H), 7.8 (dd, $J=7.6$, 1.5 Hz, 1H), 7.28 (m, 1H), 6.88 (td, $J=7.6$, 1.0 Hz, 1H), 6.69 (td, $J=7.6$, 1.5 Hz, 1H), 4.62 (s, 2H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.7 (IV), 142.6 (IV), 133.0 (III), 130.9 (III), 130.2 (III), 129.1 (2C, III+IV), 128.4 (III), 127.7 (III), 124.3 (2C, III), 124.1 (IV), 93.7 (IV), 75.0 (IV), 55.5 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 3103, 2956, 2897, 2166, 1529, 1345, 1000, 842.

5.1.17. *N*-(2-Iodo-benzyl)-4-methyl-*N*-trimethylsilanylethynyl-benzenesulfonamide 16. Yield=33%. Pale yellow solid; mp 115 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.84 (m, 2H), 7.37 (m, 5H), 7.01 (m, 1H), 4.57 (s, 2H), 2.49 (s, 3H), 0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 145.0 (IV), 139.5 (III), 136.8 (IV), 134.3 (IV), 128.9 (III), 129.8 (2C, III), 128.4 (2C, III), 128.1 (2C, III), 99.0 (IV), 95.0 (IV), 74.0 (IV), 59.6 (II), 21.8 (I), 0.0 (3C, I); IR (neat) cm^{-1}: 2954, 2159, 1364, 1247, 1164, 836, 745.

5.2. General procedure for Danheiser's method[22]

Copper iodide was purified with THF for 24 h in a Soxhlet extractor. Pyridine was distilled and degassed with argon. The amide **17** or **18** (1 mmol) was introduced in a reaction vessel, and three vacuum-argon cycles were done. Degassed pyridine (4.5 mL) was added via syringe and the temperature was lowered to 0 °C. KHMDS (0.5 M solution in toluene, 2 mL, 1 mmol, 1 equiv) was added via syringe over 4 min and the mixture was stirred during 10 min. Copper iodide (1 mmol, 1 equiv) in pyridine (2 mL) was then added in one batch through a canula, which was then rinsed with pyridine (1 mL). The temperature was raised to rt and after 2 h of stirring, the bromoalkyne (2 M solution in toluene, 1 mL, 2 equiv) was added over 1 h. The reaction was monitored by thin-layer chromatography (petroleum ether/ethylacetate 80:20). After 20 h, the reaction mixture was diluted in ether (30 mL) and washed trice with a solution of saturated aq ammonium chloride and ammonia (NH_4Cl/NH_4OH 2:1, 3×10 mL). The aqueous layer was extracted trice with ether (3×10 mL). The combined organic layers were washed with a 5% solution of copper sulfate (to remove the pyridine) and washed with brine. An acidic wash may also be done but is not compatible with certain substrates (tosylated amines for example). The organic layers were dried on magnesium sulfate and concentrated under reduced pressure to give a brown oil, which was purified on a silica gel to give the product as an oil: compounds **21**[22,23,37] or **22**, respectively, in 78 or 75% yield.

5.3. General procedure for Hsung's method[23]

The bromoalkyne (1.1 mmol, 1.1 equiv) was diluted in toluene (0.5 mL) and then the amide **17** or **18** (1 mmol, 1 equiv), potassium carbonate (2 equiv), copper sulfate pentahydrate (10 mol%) and phenantroline (20 mol%) were added. The reaction mixture was then sonicated and heated at 65 °C. The reaction was monitored by thin-layer chromatography (petroleum ether/ethylacetate 80:20). After 50 h, the reaction mixture was diluted in chloroform (30 mL), filtered through Celite and concentrated under reduced pressure to give an orange oil, which was purified on silica gel to give the product as an oil: compounds **21**[22,23,37] or **22**, respectively, in 96 and 80% yield.

5.3.1. *N*-(2-Bromobenzyl)-4-methyl-*N*-(phenylethynyl)-benzenesulfonamide 22. Yellow oil; ^1H NMR ($CDCl_3$) 400 MHz 7.55 (dd, $J=8.1$, 1.2 Hz, 1H), 7.49 (dd, $J=7.8$, 1.5 Hz, 1H), 7.37 (d, $J=8.3$ Hz, 2H), 7.31 (dt, $J=7.6$, 1.0 Hz, 1H), 7.24 (br s, 5H), 7.18 (dt, $J=7.6$, 1.5 Hz, 1H), 4.73 (s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$) 100 MHz: 145.0 (IV), 134.5 (IV), 134.0 (IV), 133.0 (III), 131.2 (III, 2C), 130.5 (III), 130.0 (III, 2C), 129.8 (III), 128.3 (III, 2C), 128.0 (III, 2C), 127.8 (III), 127.7 (III), 123.8 (IV), 122.8 (IV), 82.5 (IV), 71.3 (IV), 55.4 (II), 21.8 (I); IR (neat) cm^{-1}: 3063, 2924, 2237, 1702, 1357, 1167.

5.3.2. *N*-(2-Bromo-benzyl)-*N*-ethynyl-acrylamide 23. Yield=95%. Clear oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.59 (d, $J=8.6$ Hz, 1H), 7.29 (m, 2H), 7.17 (m, 2H), 6.56 (dd, $J=16.7$, 1.7 Hz, 1H), 5.90 (dd, $J=10.4$, 1.7 Hz, 1H), 4.91 (s, 2H), 2.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.6 (IV), 134.5 (IV), 132.9 (III), 131.6 (II), 129.4 (III), 127.6 (III), 126.3 (III), 123.6 (IV), 76.8 (IV), 62.4 (III), 51.3 (II); IR (neat) cm^{-1}: 3223, 3052, 3035, 2135, 1671, 1620. Anal. Calcd for $C_{12}H_{10}BrNO$ (264.12): C, 54.57; H, 3.82; N, 5.30. Found: C, 54.202; H, 4.29; N, 5.32.

5.3.3. Cyclohex-1-enecarboxylic acid (2-bromo-benzyl)-ethynyl-amide 24. Yield=98%. Pale yellow solid; mp 38–40 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.59 (d, $J=7.6$ Hz, 1H), 7.32 (m, 2H), 7.18 (m, 1H), 6.57 (h, $J=1.5$ Hz, 1H), 4.85 (s, 2H), 2.79 (s, 1H), 2.37 (m, 2H), 2.20 (m, 2H), 1.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 172.4 (IV), 135.0 (IV), 134.9 (III), 133.0 (III), 132.4 (IV), 129.6 (III), 129.3 (III), 127.5 (III), 123.7 (IV), 78.4 (IV), 60.90 (III), 52.1 (II), 25.4 (II), 25.1 (II), 22.0 (II), 21.5 (II); IR (neat) cm^{-1}: 3231, 3061, 3032, 2136, 1659. Anal. Calcd for $C_{16}H_{16}BrNO$ (318.21): C, 60.39; H, 5.07; N, 4.40. Found: C, 60.48; H, 5.12; N, 4.29.

5.3.4. *N*-Ethynyl-*N*-(2-iodo-benzyl)-acrylamide 25. Yield=91%. Paste; ^1H NMR ($CDCl_3$, 400 MHz): 7.86 (dd, $J=8.1$, 1.0 Hz, 1H), 7.34 (td, $J=7.7$, 1.0 Hz, 1H), 7.25 (dd, $J=7.7$, 1.5 Hz, 1H), 7.14 (dd, $J=16.9$, 10.4 Hz, 1H), 7.00 (td, $J=7.7$, 1.5 Hz, 1H), 6.57 (dd, $J=16.9$, 1.8 Hz, 1H), 5.91 (dd, $J=10.4$, 1.8 Hz, 1H), 4.84 (s, 2H), 2.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.6 (IV), 139.6 (III), 137.5 (IV), 131.7 (II), 129.5 (III), 128.7 (III), 128.5 (III),

126.3 (III), 98.7 (IV), 76.7 (IV), 62.7 (III), 55.8 (II); IR (neat) cm^{-1}: 3294, 3058, 2139, 1681, 1623. Anal. Calcd for $C_{12}H_{10}INO$ (311.12): C, 46.33; H, 3.24; N, 4.50. Found: C, 46.41; H, 3.24; N, 4.34.

5.3.5. *N*-Allyl-*N*-ethynyl-2-iodo-benzamide 26. Yield=83%. Pale yellow solid; mp 43–45 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.84 (d, J=8.1 Hz, 1H), 7.40 (td, J=7.4, 1.1 Hz, 1H), 7.32 (dd, J=7.5, 1.1 Hz, 1H), 7.13 (td, J=7.5, 1.6 Hz, 1H), 6.02 (ddt, J=6.2, 10.2, 17.0 Hz, 1H), 5.44 (dd, J=17.0, 1.0 Hz, 1H), 5.35 (d, J=10.2 Hz, 1H), 4.32 (d, J=6.2 Hz, 2H), 2.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171 (IV), 141.0 (IV), 139.1 (III), 131.0 (III), 130.7 (III), 127.9 (III), 127.7 (III), 119.6 (II), 92.1 (IV), 76.7 (IV), 61.4 (I), 50.5 (II); IR (neat) cm^{-1}: 3237, 3096, 3052, 3012, 2141, 1669, 1646. Anal. Calcd for $C_{12}H_{10}INO$ (297.09): C, 46.33; H, 3.24; N, 4.50. Found: C, 46.52; H, 3.57; N, 4.27.

5.3.6. *N*-Allyl-2-iodo-*N*-prop-1-ynyl-benzamide 27. Yield=62%. Clear oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.84 (d, J=8.1 Hz, 1H), 7.40 (td, J=7.3, 1.0 Hz, 1H), 7.33 (dd, J=7.7, 1.8 Hz, 1H), 7.10 (td, J=7.7, 1.5 Hz, 1H), 6.00 (ddt, J=6.0, 10.6, 16.9 Hz, 1H), 5.42 (dd, J=16.9, 1.3 Hz, 1H), 5.32 (dd, J=10.1, 1.0 Hz, 1H), 4.30 (d, J=6.0 Hz, 2H), 1.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.0 (IV), 141.6 (IV), 138.9 (III), 131.3 (III), 130.7 (III), 127.8 (III), 127.7 (III), 119.0 (II), 92.3 (IV), 73.7 (IV), 68.2 (IV), 50.6 (II), 3.1 (I); IR (neat) cm^{-1}: 3080, 3013, 2263, 1731, 1674.

5.3.7. [Allyl-(2-iodo-benzoyl)-amino]-propynoic acid ethyl ester 28. Yield=90%. Clear oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.87 (dd, J=8.4, 1.0 Hz, 1H), 7.44 (td, J=7.6, 1.0 Hz, 1H), 7.33 (dd, J=7.6, 1.5 Hz, 1H), 7.18 (td, J=7.6, 1.8 Hz, 1H), 5.98 (ddd, J=16.9, 10.2, 6.3 Hz, 1H), 5.46 (d, J=16.9 Hz, 1H), 5.38 (d, J=10.2 Hz, 1H), 4.35 (d, J=5.6 Hz, 2H), 4.06 (q, J=7.1 Hz, 2H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.9 (IV), 153.8 (IV), 139.7 (IV), 139.3 (III), 131.6 (III), 130.0 (III), 128.0 (III), 127.8 (III), 120.4 (II), 92.0 (IV), 82.4 (IV), 68.9 (IV), 61.5 (II), 50.7 (II), 14.0 (I); IR (neat) cm^{-1}: 3085, 2225, 1693.

Standard cyclization conditions. A degassed solution of ynamide (0.25 mmol), tributyltin hydride (0.5 mmol, 2 equiv) and AIBN (0.12 mmol, 0.5 equiv) in benzene (15 mL) was refluxed until the monitoring of the reaction by TLC showed total consumption of the starting material. Once the mixture was back to rt, aq NaOH (1 M, 15 mL) was added and stirred for 30 min. The organic phase was extracted with ethyl acetate (2×20 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by silica gel flash chromotography (pentane/ethyl acetate/triethylamine 80:20:1) afforded cyclization products. In case of ynamides in Table 2 the eluent was pentane/ethyl acetate/triethylamine 70:30:1.

Slow addition conditions. A degassed solution of tin hydride (0.5 mmol, 2 equiv) and AIBN (0.12 mmol, 0.5 equiv) in benzene (5 mL) was added over a period of 2 h via a syringe pump to a refluxing degassed solution of ynamide (0.25 mmol) in benzene (10 mL). When the addition was finished, the precedent treatment was applied to afford cyclization product.

Atom transfer conditions. A degassed solution of ynamide (0.25 mmol) and hexabutylditin (0.375 mmol, 1.5 equiv) in toluene 15 mL was refluxed and irradiated with a sun lamp (300 W) until the monitoring of the reaction by TLC showed total consumption of the starting material. The precedent treatment was applied to afford cyclization products.

5.3.8. 2,2,2-Trifluoro-1-(1-trimethylsilanylmethylene-1,3-dihydro-isoindol-2-yl)-acetamide 29. Yield=78%. Two diastereomers *Z*/*E*: 2:1; pale yellow solid; mp 56–58 °C; ^1H NMR (C_6D_6, 400 MHz): 7.80 (d, J=7.5 Hz, 1Hm), 7.56 (se, 1Hm), 7.25 (m, 1HM), 7.10 (m, 2HM+2Hm), 6.69 (m, 1HM+1Hm), 5.92 (s, 1HM), 4.39 (s, 2Hm), 4.34 (s, 2HM), 0.54 (s, 9HM), 0.42 (s, 9Hm); ^{13}C NMR (C_6D_6, 100 MHz): major compound 155.3 (q, 1C, IV, J=26.29 Hz), 148.0 (IV), 136.2 (IV), 134.8 (IV), 129.1 (III), 128.1 (III), 122.3 (III), 120.5 (III), 117.9 (q, 1C, IV, J=287.00 Hz), 109.7 (III), 52.2 (II), 1.5 (3C, I); minor compound 155.2 (q, 1C, IV, J=26.2 Hz), 149.6 (IV), 136.7 (IV), 135.0 (IV), 129.1 (III), 127.6 (III), 123.2 (III), 122.5 (III), 117.7 (q, 1C, IV, J=287.2 Hz), 109.9 (III), 51.9 (II), −0.9 (3C, I); ^{19}F NMR ($CDCl_3$, 376 MHz): −72.5 (m), −73.2 (M); IR (neat) cm^{-1}: 3043, 3024, 1696, 1248, 1132.

5.3.9. 1-Trimethylsilanyl-2,6-dihydro-3*H*-pyrido[2,1-*a*]-isoindol-4-one 30. Yield=70%. White solid; mp 136–138 °C; ^1H NMR (C_6D_6, 400 MHz): 7.79 (d, J=7.7 Hz, 1H), 7.12 (t, J=7.3 Hz, 1H), 7.05 (t, J=7.7 Hz, 1H), 6.87 (d, J=7.3 Hz, 1H), 4.75 (s, 2H), 2.32 (m, 2H), 2.23 (m, 2H), 0.35 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz): 168.2 (IV), 146.8 (IV), 139.1 (IV), 135.0 (IV), 128.4 (III), 126.8 (III), 123.8 (III), 123.3 (III), 105.5 (IV), 50.0 (II), 30.8 (II), 26.0 (II), 0.1 (3C, I); IR (neat) cm^{-1}: 3078, 3051, 3034, 1672, 1241. Anal. Calcd for $C_{15}H_{19}NOSi$: C, 69.99; H, 7.44; N, 5.44. Found: C, 69.49; H, 7.61; N, 5.08.

5.3.10. 2,6-Dihydro-3*H*-pyrido[2,1-*a*]isoindol-4-one 31. Yield=54%. Paste; ^1H NMR (C_6D_6, 400 MHz): 7.23 (d, J=7.3 Hz, 1H), 7.07 (m, 2H), 6.82 (d, J=7.4 Hz, 1H), 5.14 (t, J=4.3 Hz, 1H), 4.69 (s, 2H), 2.40 (t, J=8.3 Hz, 2H), 2.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.8 (IV), 140.5 (IV), 136.7 (IV), 133.8 (IV), 129.0 (III), 127.9 (III), 123.3 (III), 120.4 (III), 94.9 (III), 50.3 (II), 30.8 (II), 21.0 (II); IR (neat) cm^{-1}: 3071, 1727, 1644.

5.3.11. 12-Trimethylsilanyl-2,3,4,4a,7,12a-hexahydro-1*H*-isoindolo[2,1-*b*]isoquinolin-5-one 32. Yield=75%. White solid; mp 120–123 °C; ^1H NMR (C_6D_6, 400 MHz): 7.83 (d, J=7.6 Hz, 1H), 7.13 (t, J=7.6 Hz, 1H), 7.06 (t, J=7.1 Hz, 1H), 6.87 (d, J=7.6 Hz, 1H), 4.85 (AB, J_{AB}=17.0 Hz, 2H), 2.94 (m, 1H), 2.54 (m, 2H), 1.9–1.2 (m, 7H), 0.42 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz): 169.9 (IV), 145.7 (IV), 139.4 (IV), 135.3 (IV), 132.4 (IV), 128.5 (III), 127.0 (III), 123.9 (III), 123.5 (III), 50.2 (II), 40.8 (III), 40.3 (III), 28.8 (II), 26.7 (II), 25.0 (II), 22.8 (II), 0.4 (3C, I); IR (neat) cm^{-1}: 3070, 3034, 1730, 1669, 1249; MS (C.I.), m/z 312 (MH+), 269, 182.

5.3.12. 1-Trimethylsilanyl-3,4-dihydro-2*H*-pyrido[2,1-*a*]-isoindol-6-one 33. White solid; mp 128–130 °C; ^1H NMR (C_6D_6, 400 MHz): 8.09 (d, J=7.3 Hz, 1H), 7.82

(d, J=7.8 Hz, 1H), 7.21 (td, J=7.3, 1.2 Hz, 1H), 7.12 (td, J=7.3, 0.7 Hz, 1H), 3.65 (t, J=5.8 Hz, 2H), 2.03 (t, J=6.0 Hz, 2H), 1.39 (m, 2H), 0.34 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): 166.1 (IV), 140.2 (IV), 135.0 (IV), 131.1 (III), 131.1 (IV), 128.7 (III), 123.5 (III), 123.3 (III), 119.9 (IV), 38.9 (II), 28.6 (II), 22.1 (II), 0.3 (3C, I); IR (neat) cm^{-1}: 3082, 3058, 3022, 1685, 1281.

5.3.13. 3,4-Dihydro-2*H*-pyrido[2,1-*a*]isoindol-6-one 34. Paste; ^{1}H NMR (C_6D_6, 400 MHz): 8.00 (dt, J=7.6, 1.0 Hz, 1H), 7.31 (d, J=7.6 Hz, 1H), 7.21 (td, J=8.6, 1.3 Hz, 1H), 7.14 (td, J=7.6, 1.0 Hz, 1H), 5.34 (t, J=4.6 Hz, 1H), 3.58 (m, 2H), 1.86 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz): 164.9 (IV), 135.5 (IV), 135.0 (IV), 130.8 (III), 130.6 (IV), 128.6 (III), 128.1 (III), 123.0 (III), 119.2 (III), 102.7 (III), 38 (II), 22.1 (II), 21.2 (II); IR (neat) cm^{-1}: 3053, 1690, 1664.

5.3.14. 1-Methyl-3,4-dihydro-2*H*-pyrido[2,1-*a*]isoindol-6-one 35. Yield=84%. White solid; mp 98–100 °C; ^{1}H NMR (C_6D_6, 400 MHz): 8.14 (d, J=7.4 Hz, 1H), 7.53 (d, J=7.6 Hz, 1H), 7.25 (m, 1H), 7.16 (t, J=7.3 Hz, 1H), 3.61 (m, 2H), 1.80 (s, 3H), 1.76 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz): 164.4 (IV), 135.4 (IV), 131.2 (IV), 130.7 (III), 129.4 (IV), 127.7 (III), 123.3 (III), 122.6 (III), 116.8 (IV), 37.7 (II), 30.3 (II), 21.2 (II), 18.5 (I); IR (neat) cm^{-1}: 3058, 3029, 1662.

5.3.15. 6-Oxo-2,3,4,6-tetrahydro-pyrido[2,1-*a*]isoindole-1-carboxylic acid ethyl ester 36. Yield=45%. White solid; mp 62–65 °C; ^{1}H NMR (C_6D_6, 400 MHz): 9.15 (d, J=8.2 Hz, 1H), 7.98 (dt, J=7.6, 1.0 Hz, 1H), 7.33 (td, J=8.1, 1.3 Hz, 1H), 7.14 (td, J=7.3, 0.7 Hz, 1H), 4.17 (q, J=7.3 Hz, 2H), 3.44 (m, 2H), 2.33 (t, J=6.0 Hz, 2H), 1.27 (m, 2H), 1.13 (t, J=7.1 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz): 166.5 (IV), 165.5 (IV), 141.6 (IV), 134.4 (IV), 132.1 (III), 130.9 (IV), 130.1 (III), 127.3 (III), 122.7 (III), 109.6 (IV), 60.2 (II), 38.1 (II), 25.3 (II), 20.1 (II), 14.1 (I); IR (neat) cm^{-1}: 3073, 1693, 1603.

5.3.16. 12-Trimethylsilanyl-7*H*-isoindolo[2,1-*b*]isoquinolin-5-one 37. Yield=67%. Yellow solid; mp 132–134 °C; ^{1}H NMR (C_6D_6, 400 MHz): 9.01 (dd, J=8.1, 1.5 Hz, 1H), 7.87 (dd, J=7.1, 3.0 Hz, 2H), 7.42 (td, J=6.6, 1.5 Hz, 1H), 7.31 (t, J=7.1 Hz, 1H), 7.10 (m, 2H), 6.93 (d, J=7.6 Hz, 1H), 4.85 (s, 2H), 0.56 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz): 161.1 (IV), 149.8 (IV), 142.8 (IV), 140.3 (IV), 136.1 (IV), 131.1 (III), 129.7 (III), 128.7 (III), 128.2 (III), 127.1 (III), 126.7 (III), 126.2 (III), 123.7 (III), 107.3 (IV), 52.5 (II), 3.7 (3C, I); IR (neat) cm^{-1}: 3053, 3035, 1644, 1603, 1249.

5.3.17. 4-Methoxy-12-trimethylsilanyl-7*H*-isoindolo-[2,1-*b*]isoquinolin-5-one 38. Yield=54%. Yellow solid; mp 135–136 °C; ^{1}H NMR (C_6D_6, 200 MHz): 8.68 (d, 1H, J=8.0 Hz), 7.99 (d, 1H, J=8.0 Hz), 7.32–6.92 (m, 4H), 6.69 (d, 1H, J=7.8 Hz), 4.88 (s, 2H), 3.41 (s, 3H), 0.52 (s, 9H); ^{13}C NMR (C_6D_6, 50 MHz): 160.6 (IV), 155.9 (IV), 149.7 (IV), 139.8 (IV), 136.4 (IV), 134.1 (IV), 129.5 (III), 126.8 (III), 126.5 (III), 126.4 (III), 123.3 (III), 119.9 (III), 111.5 (III), 104.1 (IV), 54.1 (I), 52.3 (II), 3.1 (3C, I); IR (neat) cm^{-1}: 3069, 3033, 1713, 1645, 1234. Anal. Calcd for $C_{20}H_{21}NO_2Si$ (335.47): C, 71.60; H, 6.31; N, 4.18. Found: C, 71.49; H, 6.41; N, 4.09.

5.3.18. 12-Trimethylsilanyl-5*H*-isoindolo[2,1-*b*]isoquinolin-7-one 39. Yield=46%. Yellow solid; mp 126–128 °C; ^{1}H NMR (C_6D_6, 400 MHz): 7.98 (d, 1H, J=7.1 Hz), 7.75 (d, 1H, J=7.6 Hz), 7.34 (d, 1H, J=7.0 Hz), 7.15 (m, 3H), 7.02 (td, 1H, J=7.6, 1.3 Hz), 6.86 (d, 1H, J=7.6 Hz), 4.73 (s, 2H), 0.50 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz): 165.9 (IV), 144.1 (IV), 136.9 (IV), 135.7 (IV), 131.0 (IV), 130.5 (III), 130.0 (IV), 129.3 (III), 128.4 (III), 126.8 (III), 126.8 (III), 126.6 (III), 124.5 (III), 123.4 (III), 117.2 (IV), 42.8 (II), 2.0 (3C, I); IR (neat) cm^{-1}: 3058, 3016, 1691, 1251.

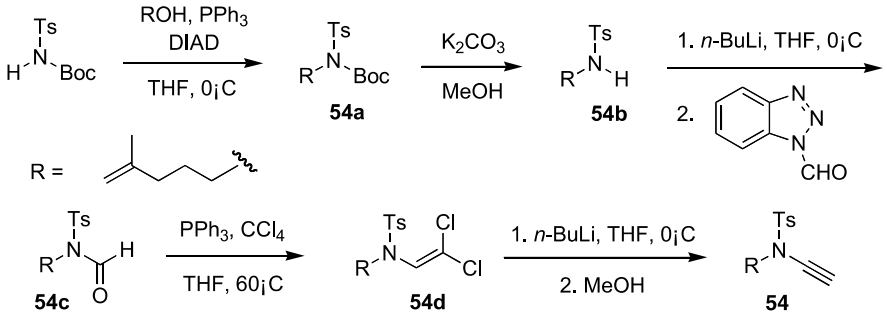
5.3.19. 2-Benzyl-3-trimethylsilanylmethylene-2,3-dihydro-isoindol-1-one 40. Yield=57%. Two diastereomers (1/1): paste; ^{1}H NMR (C_6D_6, 400 MHz): 8.05 (d, J=7.3 Hz, 1H), 7.95 (d, J=7.6 Hz, 1H), 7.81 (d, J=7.8 Hz, 1H), 7.43 (d, J=7.6 Hz, 1H), 7.30–7.00 (m, 14H), 5.58 (s, 1H), 5.28 (s, 1H), 5.19 (s, 2H), 4.95 (s, 2H), 0.27 (s, 9H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.4 (IV), 167.1 (IV), 146.6 (IV), 145.8 (IV), 138.1 (IV), 137.1 (IV), 136.7 (IV), 136.3 (IV), 132.1 (III), 131.7 (III), 130.5 (IV), 129.4 (III), 129.3 (III), 128.6 (4C, III), 128.4 (IV), 127.2 (III), 127.1 (2C, III), 127.0 (III), 125.8 (2C, III), 123.5 (III), 123.1 (III), 122.9 (III), 120.0 (III), 106.8 (III), 102.8 (III), 44.0 (II), 42.7 (II), 1.2 (3C, I), 0.3 (3C, I); IR (neat) cm^{-1}: 3087, 3063, 3031, 1705, 1606, 1249.

5.3.20. 11-Trimethylsilanyl-isoindolo[2,1-*a*]indol-6-one 41. Yield=62%. Yellow solid; mp 139–142 °C; ^{1}H NMR (C_6D_6, 400 MHz): 8.26 (d, J=7.8 Hz, 1H), 7.65 (m, 2H), 7.47 (d, J=7.6 Hz, 1H), 7.18 (td, J=7.6, 1.0 Hz, 1H), 7.08 (td, J=8.0, 1.0 Hz, 1H), 7.01 (td, J=7.5, 1.0 Hz, 1H), 6.83 (t, J=7.3 Hz, 1H), 0.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.5 (IV), 144.3 (IV), 139.1 (IV), 135.5 (IV), 134.3 (IV), 133.9 (IV), 133.6 (III), 128.6 (III), 126.1 (III), 125.3 (III), 123.6 (III), 123.5 (III), 122.6 (III), 116.0 (IV), 113.2 (III), 0.6 (3C, I); IR (neat) cm^{-1}: 3051, 1763, 1725, 1245.

5.3.21. 2-Phenyl-3-trimethylsilanylmethylene-2,3-dihydro-isoindol-1-one 42. Yield=71%. Two diastereomers *Z*/*E*: 2:1; yellow solid; mp 136–138 °C; ^{1}H NMR (C_6D_6, 400 MHz): 8.06 (d, J=7.6 Hz, 1Hm), 7.97 (d, J=7.6 Hz, 1HM), 7.93 (d, J=7.8 Hz, 1Hm), 7.43 (d, J=7.8 Hz, 1HM), 7.32–7.30 (m, 2HM+2Hm), 7.24–7.08 (m, 5HM+5Hm), 5.59 (s, 1HM), 5.45 (s, 1Hm), 0.29 (s, 9Hm), −0.07 (s, 9HM); ^{13}C NMR (C_6D_6, 100 MHz): major compound 167.3 (IV), 147.7 (IV), 138.5 (IV), 136.9 (IV), 132.0 (III), 129.4 (2C, III), 129.1 (2C, III), 127.9 (2C, III), 123.3 (III), 119.9 (III), 102.8 (III), 0.1 (3C, I); IR (neat) cm^{-1}: 3062, 3043, 1713, 1609, 1247; minor compound 165.8 (IV), 148.3 (IV), 136.4 (IV), 135.1 (IV), 131.6 (III), 129.5 (2C, III), 129.3 (2C, III), 129.2 (2C, III), 123.8 (III), 123.0 (III), 105.1 (III), 0.0 (3C, I); IR (neat) cm^{-1}: 3062, 3043, 1713, 1609, 1247. IEMS: *m*/*z* (%)=293 [(M^+), 3], 276 [M^+−17, 100], 232 [M^+−63, 17].

5.4. Svnthesis of cycloisomerization precursors: a representative example (Scheme 10)

5.4.1. *N-tert*-Butoxycarbonyl-*N*-(4-methylpent-4-enyl)-4-methylbenzenesulfonamide 54a. Ts-NH–Boc (12.25 g,



Scheme 10.

45.2 mmol, 1 equiv), PPh_3 (11.86 g, 45.2 mmol, 1 equiv) and 4-methylpent-4-en-1-ol (4.52 g, 45.2 mmol, 1 equiv) were introduced in 100 mL of THF. The mixture was cooled to 0 °C and 8.96 mL (45.2 mmol, 1 equiv) of DIAD were added dropwise. After stirring for 5 min, the mixture was allowed to warm up to rt and stirred for 1 h. The solvent was removed and the residue was purified by flash column chromatography on silica gel (PE/Et_2O 9:1–4:1) to give **54a** (14.43 g, 90%) as a yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.79 (d, $J=8.2$ Hz, 2H), 7.31 (d, $J=8.2$ Hz, 2H), 4.76 (br s, 2H), 3.83 (t, $J=7.6$ Hz, 2H), 2.44 (s, 3H), 2.08–2.12 (m, 2H), 1.91–1.95 (m, 2H), 1.77 (s, 3H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.9 (IV), 144.4 (IV), 144.0 (IV), 137.5 (IV), 129.2 (2C, III), 127.7 (2C, III), 110.4 (II), 83.9 (IV), 46.9 (II), 34.7 (II), 31.8 (II), 27.8 (3C, I), 22.2 (I), 21.5 (I); IR (neat) cm^{-1}: 2984, 1718, 1649, 1350, 1152. Anal. Calcd for $C_{18}H_{27}O_4NS$ (353.28): C, 61.17; H, 7.69; N, 3.96. Found: C, 61.00; H, 7.77; N, 4.10.

5.4.2. *N*-(4-Methylpent-4-enyl)-4-methylbenzenesulfonamide 54b. Consistent with literature (Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172).

In a flask containing a solution of **54a** (13.94 g, 39.49 mmol, 1 equiv) in methanol (400 mL) was added K_2CO_3 (27.29 g, 197.45 mmol, 5 equiv). After refluxing for 3 h, water (100 mL) was introduced and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to give **54b** (9.99 g, 100%) as a yellow oil.

5.4.3. *N*-Formyl-*N*-(4-methylpent-4-enyl)-4-methylbenzenesulfonamide 54c. Under argon, *n*-BuLi (18.8 mL, 2.3 M solution in hexane, 43.16 mmol, 1.1 equiv) was added to a solution of **54b** (9.93 g, 39.23 mmol, 1 equiv) in THF (200 mL) at 0 °C. After stirring for 5 min, *N*-formylbenzotriazole (6.92 g, 47.08 mmol, 1.2 equiv) was added, and the mixture was stirred at rt for 1 h. After addition of saturated $NaHCO_3$ aq, the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O 9:1–4:1) to give **54c** (9.85 g, 89%) as a colourless oil; ^1H NMR ($CDCl_3$, 200 MHz): 9.09 (s, 1H), 7.74 (d, $J=8.0$ Hz, 2H), 7.36 (d, $J=8.0$ Hz, 2H), 4.69 (br s, 1H), 4.62 (br s, 1H), 3.40 (t, $J=7.8$ Hz, 2H), 2.44 (s, 3H), 1.95 (t, $J=8.3$ Hz, 2H), 1.58–1.70 (m, 2H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): 161.2 (IV), 145.4 (IV), 144.0 (IV), 135.0 (IV), 130.3 (2C, III), 127.3 (2C, III), 110.6 (II), 42.4 (II), 34.6 (II), 25.7 (II), 22.1 (I), 21.6 (I); IR (neat) cm^{-1}: 3072, 2935, 1697, 1650, 1596, 1355, 1161. Anal. Calcd for $C_{14}H_{19}O_3NS$ (281.37): C, 59.77; H, 6.80; N, 4.98. Found: C, 59.67; H, 6.89; N, 5.15.

5.4.4. *N*-(2,2-Dichlorovinyl)-*N*-(4-methylpent-4-enyl)-4-methylbenzenesulfonamide 54d. To a solution of **54c** (9.79 g, 34.83 mmol, 1 equiv) and PPh_3 (27.41 g, 104.49 mmol, 3 equiv) in THF (350 mL) at 60 °C was added 33.7 mL of CCl_4 (348.29 mmol, 10 equiv) over 6 h. After addition of saturated $NaHCO_3$ aq, the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O 9:1, then PE/EA 9:1–4:1) to give **54d** (12.12 g, 100%) as a yellow solid; mp 85 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.67 (d, $J=8.1$ Hz, 2H), 7.31 (d, $J=8.1$ Hz, 2H), 6.25 (s, 1H), 4.71 (br s, 1H), 4.65 (br s, 1H), 3.29 (t, $J=7.3$ Hz, 2H), 2.42 (s, 3H), 2.01 (t, $J=7.5$ Hz, 2H), 1.68 (s, 3H), 1.60–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.4 (IV), 144.2 (IV), 135.4 (IV), 130.0 (2C, III), 127.3 (2C, III), 125.0 (III), 124.8 (IV), 110.7 (II), 49.0 (II), 34.6 (II), 26.4 (II), 22.4 (I), 21.6 (I); IR (neat) cm^{-1}: 3067, 2969, 1650, 1598, 1353, 1164.

5.4.5. Ynamide 54. Under argon, *n*-BuLi (9.57 mL, 2.3 M solution in hexane, 22 mmol, 2.2 equiv) was added to a solution of **54d** (3.48 g, 10 mmol, 1 equiv) in anhydrous THF (50 mL) at −78 °C and the mixture was stirred during 45 min, 80 μL (2 mmol, 0.2 equiv) of MeOH were then added and the mixture was allowed to warm up to rt over 1 h 30. After addition of saturated $NaHCO_3$ aq, the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (pentane/EA/NEt_3 90:10:1) to give **54** (1.97 g, 71%) as a yellow solid; mp 49 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.77 (d, $J=7.8$ Hz, 2H), 7.33 (d, $J=7.8$ Hz, 2H), 4.70 (s, 1H), 4.64 (s, 1H), 3.27 (t, $J=6.4$ Hz, 2H), 2.74 (s, 1H), 2.41 (s, 3H), 1.98–2.01 (m, 2H), 1.72–1.80 (m, 2H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.7 (IV), 144.0 (IV), 134.4 (IV), 129.7 (2C, III), 127.5 (2C, III), 110.6 (II), 75.9 (IV), 59.1 (III), 50.7 (II), 34.0 (II), 25.4 (II), 22.4 (I), 21.5 (I); IR (neat) cm^{-1}: 3294, 3073, 2933, 2132, 1650, 1596, 1362, 1166. Anal. Calcd for $C_{15}H_{19}O_2NS$ (277.38): C, 64.95; H, 6.90; N, 5.05. Found: C, 64.82; H, 7.05; N, 5.09.

Ynamides **45**, **47**, **49** and **57** were prepared according to this method.

5.4.6. Ynamide 45. Consistent with literature (Ref. 28b). Yield=82%.

Anal. Calcd for $C_{14}H_{17}O_2NS$ (263.36): C, 63.85; H, 6.51; N, 5.32. Found: C, 63.73; H, 6.70; N, 5.38.

5.4.7. Ynamide 47. Consistent with literature (Ref. 28b). Yield=69%. White solid; mp 53 °C.

5.4.8. Ynamide 49. Yield=56%. White solid; mp 38 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.82 (d, J=4.2 Hz, 2H), 7.37 (d, J=4.2 Hz, 2H), 5.81 (ddt, J=17.0, 10.1, 6.4 Hz, 1H), 4.92–5.07 (m, 2H), 3.15 (s, 2H), 2.70 (s, 1H), 2.46 (s, 3H), 1.99–2.11 (m, 2H), 1.41–1.50 (m, 2H), 1.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): 144.7 (IV), 138.9 (III), 134.3 (IV), 129.7 (2C, III), 127.8 (2C, III), 114.2 (II), 78.7 (IV), 61.5 (II), 58.3 (III), 38.8 (II), 35.7 (IV), 28.2 (II), 25.2 (2C, I), 21.6 (I); IR (neat) cm^{-1}: 3276, 3081, 2968, 2133, 1643, 1598, 1355, 1168. Anal. Calcd for $C_{17}H_{23}O_2NS$ (305.44): C, 66.85; H, 7.59; N, 4.59. Found: C, 66.67; H, 7.78; N, 4.62.

5.4.9. Ynamide 57. Yield=66%. White solid; mp 77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.80 (d, J=8.2 Hz, 2H), 7.35 (d, J=8.2 Hz, 2H), 4.88 (br s, 1H), 4.67 (br s, 1H), 3.16 (s, 2H), 2.68 (s, 1H), 2.45 (s, 3H), 2.07 (s, 2H), 1.78 (s, 3H), 1.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.8 (IV), 142.5 (IV), 134.5 (IV), 129.9 (2C, III), 128.0 (2C, III), 115.3 (II), 79.0 (IV), 63.0 (II), 58.5 (III), 48.0 (II), 36.7 (IV), 25.6 (3C, I), 21.8 (I); IR (neat) cm^{-1}: 3274, 3070, 2964, 2133, 1638, 1597, 1355, 1168. Anal. Calcd for $C_{17}H_{23}O_2NS$ (305.44): C, 66.85; H, 7.59; N, 4.59. Found: C, 67.00; H, 7.82; N, 4.38.

5.4.10. Ynamide 59. To a solution of LiHMDS (343 mg, 2.13 mmol, 1.3 equiv) in THF (8 mL) at −78 °C was added *n*-BuLi (0.92 mL, 2.3 M solution in hexane, 2.13 mmol, 1.3 equiv). The mixture was stirred for 10 min, then a solution of ynamide **47** (476 mg, 1.64 mmol, 1 equiv) in THF (8 mL) was canulated. The reaction medium was allowed to warm up to −40 °C and was stirred for 1 h, and then MeI (0.51 mL, 8.18 mmol, 5 equiv) was slowly added. The mixture was stirred for 30 min at −40 °C, then allowed to warm up to rt and stirred for 20 h. To the mixture was added saturated $NaHCO_3$ aq, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (pentane/EA 95:5) to give **59** (420 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.76 (d, J=8.2 Hz, 2H), 7.33 (d, J=8.2 Hz, 2H), 5.80 (ddt, J=16.9, 10.4, 7.3 Hz, 1H), 4.99–5.06 (m, 2H), 3.06 (s, 2H), 2.44 (s, 3H), 2.08 (d, J=7.6 Hz, 2H), 1.84 (s, 3H), 0.98 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.3 (IV), 134.7 and 134.6 (IV+III), 129.7 (2C, III), 127.8 (2C, III), 117.8 (II), 74.9 (IV), 64.8 (IV), 61.8 (II), 44.5 (II), 35.8 (IV), 25.2 (2C, I), 21.7 (I), 3.3 (I); IR (neat) cm^{-1}: 3074, 2966, 2259, 1638, 1597, 1363, 1170. Anal. Calcd for $C_{17}H_{23}O_2NS$ (305.44): C, 66.85; H, 7.59; N, 4.59. Found: C, 67.21; H, 7.69; N, 4.26.

5.5. General procedure for cycloisomerizations

In a dry schlenk under argon was introduced 0.5 mmol of ynamide in 20 mL of anhydrous toluene. The reaction medium was degassed by the freeze-pump-thaw method and the reaction vessel was plunged in a pre-heated oil bath (80 °C). $PtCl_2$ (7 mg, 0.025 mmol, 0.05 equiv) was then added, and the mixture was stirred until the IR spectrum indicated the vanishing of the triple bond. The solvent was removed and the residue was purified by flash chromatography (PE/Et_2O/NEt_3 85:15:1) to give the desired cyclization product.

5.5.1. Dienamide 44. Consistent with literature (Ref. 28b). Yield=98%.

5.5.2. Bicyclic enamide 46. Yield=44%. Pale yellow oil; ^{1}H NMR (C_6D_6, 400 MHz): 7.72 (d, J=8.1 Hz, 2H), 6.77 (d, J=8.1 Hz, 2H), 3.20–3.22 (m, 2H), 3.09 (quint., J=3.2 Hz, 2H), 2.15–2.18 (m, 2H), 1.86 (s, 3H), 1.35–1.38 (m, 2H), 1.18–1.21 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz): 141.3 (IV), 136.8 (IV), 134.2 (IV), 129.8 (2C, III), 127.6 (2C, III), 122.3 (IV), 45.7 (II), 33.1 (II), 28.7 (II), 22.5 (II), 22.0 (II), 21.1 (I); IR (neat) cm^{-1}: 3074, 2920, 1691, 1597, 1353, 1166.

5.5.3. Bicyclic enamide 48. Yield=71%. Pale yellow oil; ^{1}H NMR (C_6D_6, 400 MHz): 7.76 (d, J=4.2 Hz, 2H), 6.79 (d, J=8.2 Hz, 2H), 3.11 (m, J=2.8 Hz, 2H), 2.94 (s, 2H), 2.20 (br s, 2H), 1.84 (s, 3H), 1.31 (br s, 2H), 0.69 (s, 6H); ^{13}C NMR (C_6D_6, 100 MHz): 143.1 (IV), 137.2 (IV), 132.6 (IV), 129.8 (2C, III), 127.6 (2C, III), 118.9 (IV), 55.9 (II), 36.6 (II), 32.0 (II), 31.6 (IV), 28.5 (II), 26.6 (2C, I), 21.1 (I); IR (neat) cm^{-1}: 2958, 2927, 1696, 1598, 1356, 1163.

5.6. General one-pot procedure (cycloisomerization–ozonolysis)

In a dry schlenk under argon was introduced 0.5 mmol of ynamide in 20 mL of anhydrous toluene. The reaction medium was degassed by the freeze-pump-thaw method and the reaction vessel was plunged in a pre-heated oil bath (80 °C). $PtCl_2$ (7 mg, 0.025 mmol, 0.05 equiv) was then added, and the mixture was stirred until the IR spectrum indicated the end of the reaction. The solvent was removed and CH_2Cl_2 (20 mL) was added. The mixture was cooled down to −78 °C and O_3 was allowed to bubble in the solution until the mixture becomes blue. One millilitre of SMe_2 was then added and the mixture was allowed to warm up to rt over 2 h. The solvent was removed and the residue was purified by flash chromatography (pentane/EA 9:1–1:1) to give the desired lactam.

5.6.1. Ketolactam 50. Yield=20%. Pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.91 (d, J=8.2 Hz, 2H), 7.35 (d, J=8.2 Hz, 2H), 4.00 (t, J=5.7 Hz, 2H), 2.68–2.76 (m, 4H), 2.54 (t, J=6.4 Hz, 2H), 2.46 (s, 3H), 2.13–2.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 211.4 (IV), 172.3 (IV), 145.3 (IV), 135.6 (IV), 129.4 (2C, III), 129.3 (2C, III), 46.6 (II), 46.6 (II), 37.8 (II), 33.0 (II), 27.9 (II), 21.9 (I); IR (neat) cm^{-1}: 2924, 2854, 1694, 1597, 1340, 1157; HRMS: m/z calcd for $C_{14}H_{17}O_4NS$ (MH^+) 318.0776; found 318.0792.

5.6.2. Ketolactam 51. Yield=37%. Pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.84 (d, J=8.2 Hz, 2H), 7.29 (d, J=8.2 Hz, 2H), 3.87 (br s, 2H), 2.65 (s, 4H), 2.44 (s, 2H), 2.42 (s, 3H), 1.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz):

208.5 (IV), 172.7 (IV), 145.0 (IV), 136.1 (IV), 129.3 (2C, III), 129.2 (2C, III), 56.5 (II), 51.0 (II), 43.7 (II), 37.5 (IV), 32.5 (II), 27.2 (2C, I), 21.8 (I); IR (neat) cm^{-1}: 2966, 1698, 1597, 1345, 1167.

5.6.3. Ketolactam 52. Yield=24%. Pale yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.79 (d, J=8.2 Hz, 2H), 7.28 (d, J=8.2 Hz, 2H), 3.74 (s, 2H), 2.60–2.67 (m, 4H), 2.47 (t, J=6.7 Hz, 2H), 2.40 (s, 3H), 1.66 (t, J=6.7 Hz, 2H), 1.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 212.6 (IV), 174.3 (IV), 144.9 (IV), 136.2 (IV), 129.4 (2C, III), 129.1 (2C, III), 54.7 (II), 39.7 (II), 36.9 (II), 36.6 (IV), 33.9 (II), 31.3 (II), 26.8 (2C, I), 21.8 (I); IR (neat) cm^{-1}: 2957, 2871, 1688, 1596, 1348, 1164.

5.7. General one-pot procedure (cycloisomerization–hydrolysis)

In a dry schlenk under argon was introduced 0.5 mmol of ynamide in 20 mL of anhydrous toluene. The reaction medium was degassed during 10 min. 7 mg of $PtCl_2$ (0.025 mmol, 0.05 equiv) were added and the reaction vessel was plunged in a pre-heated oil bath (80 °C). At the end of 10 min, 7 mg of $PtCl_2$ (0.025 mmol, 0.05 equiv) were added. The mixture was stirred until the IR spectrum indicated the end of the reaction. Then, the mixture was quickly cooled to rt with a water bath, and 2.5 mL (2.5 mmol, 5 equiv) of HCl 1 M were added with 20 mL of ethyl acetate. The resulting mixture was stirred during 2 h. The mixture was then neutralized with a saturated solution of $NaHCO_3$, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/EA 6:4) to give the desired cyclobutanone.

5.7.1. Cyclobutanone 53. Yield=65%. ^1H NMR ($CDCl_3$, 400 MHz): 7.73 (d, J=8.5 Hz, 2H), 7.31 (d, J=8.5 Hz, 2H), 4.63 (t, J=6.3 Hz, 1H), 3.22 (m, 1H), 2.83–3.08 (m, 4H), 2.42 (s, 3H), 2.16 (m, 1H), 1.47–1.66 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 212.1 (IV), 143.4 (IV), 136.8 (IV), 129.7 (2C, III), 127.0 (2C, III), 59.6 (III), 44.4 (II), 42.8 (II), 27.1 (II), 26.4 (II), 21.5 (I), 16.8 (I); IR (neat) cm^{-1}: 3282, 2925, 1772, 1598, 1325, 1157.

5.7.2. Cyclobutanone 55. Yield=54%. ^1H NMR ($CDCl_3$, 400 MHz): 7.73 (d, J=7.9 Hz, 2H), 7.29 (d, J=7.9 Hz, 2H), 5.22 (t, J=6.1 Hz, 1H), 2.85–3.02 (m, 4H), 2.41 (s, 3H), 1.81 (m, 1H), 1.68 (m, 1H), 1.37–1.56 (m, 4H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 215.7 (IV), 143.4 (IV), 136.9 (IV), 129.7 (2C, III), 127.1 (2C, III), 63.4 (IV), 43.3 (II), 42.2 (II), 32.8 (II), 24.7 (II), 24.0 (II), 21.5 (I), 20.4 (I); IR (neat) cm^{-1}: 3277, 2925, 1769, 1598, 1325, 1155. Anal. Calcd for $C_{15}H_{21}O_3NS$ (295.40): C, 60.99; H, 7.17; N, 4.74. Found: C, 61.01; H, 7.27; N, 4.55.

5.7.3. Cyclobutanone 56. Yield=85%. ^1H NMR ($CDCl_3$, 400 MHz): 7.74 (d, J=8.1 Hz, 2H), 7.30 (d, J=4.1 Hz, 2H), 5.22 (t, J=7.2 Hz, 1H), 3.25 (m, 1H), 3.04 (m, 1H), 2.85 (m, 1H), 2.66 (ABX, 1H), 2.58 (ABX, 1H), 2.22 (m, 1H), 1.73 (dd, J=14.6, 6.8 Hz, 1H), 1.58 (m, 1H), 1.30 (dd, J=14.6, 6.4 Hz, 1H), 0.91 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 212.6 (IV), 143.3 (IV), 137.3 (IV), 129.8 (2C, III), 127.1 (2C, III), 56.4 (III), 52.6 (II), 44.7 (II), 39.0 (II), 34.1 (IV), 26.1 (I), 24.9 (I), 21.6 (I), 18.9 (II); IR (neat) cm^{-1}: 3281, 3064, 2959, 1772, 1598, 1327, 1157. Anal. Calcd for $C_{16}H_{23}O_3NS$ (309.42): C, 62.11; H, 7.48; N, 4.53. Found: C, 61.97; H, 7.58; N, 4.51.

5.7.4. Aminal 58. Yield=76%. ^1H NMR ($CDCl_3$, 400 MHz): 7.81 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 3.33 (s, 1H), 3.01 (d, J=12.9 Hz, 1H), 2.81 (m, 1H), 2.75 (d, J=12.9 Hz, 1H), 2.45 (s, 3H), 2.35 (m, 1H), 1.72 (m, 1H), 1.52 (m, 1H), 1.35 (d, J=14.4 Hz, 1H), 1.27 (d, J=14.4 Hz, 1H), 1.17 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 143.4 (IV), 137.8 (IV), 129.5 (2C, III), 127.7 (2C, III), 87.3 (IV), 52.1 (II), 45.7 (II), 44.2 (IV), 33.8 (II), 31.4 (IV), 29.2 (I), 28.1 (II), 27.8 (I), 24.7 (I), 21.6 (I); IR (neat) cm^{-1}: 3506, 3027, 2958, 1603, 1347, 1163.

5.7.5. Cyclobutanone 60. Yield=70%. ^1H NMR ($CDCl_3$, 400 MHz): 7.74 (d, J=8.2 Hz, 2H), 7.29 (d, J=8.2 Hz, 2H), 5.25 (t, J=7.1 Hz, 1H), 3.14–3.30 (m, 2H), 2.65 (ABX, 1H), 2.60 (ABX, 1H), 2.41 (s, 3H), 1.82 (t, J=8.1 Hz, 2H), 1.69 (dd, J=14.5, 7.1 Hz, 1H), 1.37 (dd, J=14.5. 7.1 Hz. 1H), 1.18 (d, J=7.6 Hz, 3H), 0.88 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 216.8 (IV), 143.3 (IV), 137.1 (IV), 129.7 (2C, III), 127.0 (2C, III), 53.5 (III), 52.7 (II), 52.2 (III), 39.8 (II), 34.2 (II), 31.2 (II), 25.8 (I), 24.9 (I), 21.6 (I), 15.3 (I); IR (neat) cm^{-1}: 3283, 2960, 1768, 1599, 1327, 1158.

5.7.6. Cyclobutanone 61. Yield=40%. ^1H NMR ($CDCl_3$, 400 MHz): 7.73 (d, J=4.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 4.78 (t, J=6.9 Hz, 1H), 3.18 (m, 1H), 3.00 (m, 1H), 2.87 (m, 1H), 2.59–2.70 (ABX, 2H), 2.42 (s, 3H), 2.15 (m, 1H), 1.56 (m, 1H), 1.51 (m, 1H), 1.35 (m, 1H), 1.23–1.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 212.5 (IV), 143.4 (IV), 137.1 (IV), 129.9 (2C, III), 127.2 (2C, III), 60.7 (III), 52.6 (II), 44.6 (II), 36.4 (II), 33.8 (IV), 25.0 (I), 23.8 (II), 21.7 (I), 16.9 (II); IR (neat) cm^{-1}: 3284, 2958, 1773, 1598, 1326, 1158.

Acknowledgements

Authors' thanks go to Pierre Fabre Laboratories, which paid for the grants of Frédéric Marion (CIFRE) and Aurore Servais (BDI co-financed by CNRS) and to Institut Universitaire de France for general support of this work.

References and notes

1. Ficini, J. *Tetrahedron* **1976**, *32*, 1449–1486.
2. Zaugg, H. E.; Swett, L. R.; Stone, G. R. *J. Org. Chem.* **1958**, *23*, 1389–1390.
3. Wolf, V.; Kowitz, F. *Ann.* **1960**, *638*, 33–42.
4. Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 77–78 see also pages 767–778.
5. Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575–7606.
6. Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 917–918.

7. Brückner, D. *Synlett* **2000**, 1402–1404.
8. Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459–466.
9. Joshi, R. V.; Xu, Z.-Q.; Ksebati, M. B.; Kessel, D.; Corbett, T. H.; Drach, J. C.; Zemlicka, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1089–1098.
10. Zaugg, H. E.; Swett, L. R.; Stone, G. R. *J. Org. Chem.* **1958**, *23*, 1389–1390.
11. (a) Galy, J. P.; Elguero, J.; Vincent, E. J.; Barbe, J. *Synthesis* **1979**, 944–946. (b) Mahamoud, A.; Galy, J. P.; Vincent, E. J.; Barbe, J. *Synthesis* **1981**, 917–918. (c) Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852–856.
12. Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J.; Mulder, J. A.; Xiong, H. *Org. Lett.* **1999**, 1237–1240.
13. Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, 2417–2420.
14. Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489–492.
15. Witulski, B.; Gößmann, M. *Synlett* **2000**, 1793–1797.
16. Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A. *Tetrahedron Lett.* **1985**, *26*, 4141–4144.
17. (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368–2369. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379–1390.
18. Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.
19. Schottelius, M. J.; Chen, P. *Helv. Chim. Acta* **1998**, *81*, 2341–2347.
20. Novikov, M. S.; Khlebnikov, A. F.; Kostikov, R. R. *Zhurnal Organicheskoi Khimii* **1991**, *27*, 1794–1795.
21. Fromont, C.; Masson, S. *Tetrahedron* **1999**, *55*, 5405–5418.
22. Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011–4014.
23. Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151–1154.
24. (a) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281–3284. (b) Witulski, B.; Stengel, T.; Fernandèz-Hernandèz, J. M. *Chem. Commun.* **2000**, 1965–1966. (c) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426–2430.
25. (a) Rainier, J. D.; Imbroglio, J. E. *J. Org. Chem.* **2000**, *65*, 7272–7276. (b) Witulski, B.; Gößmann, M. *Chem. Commun.* **1999**, 1879–1880. (c) Shen, L.; Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353–9358.
26. Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681–3684.
27. (a) Witulski, B.; Lumtscher, J.; Bergstraber, U. *Synlett* **2003**, 708–710. (b) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. *Org. Lett.* **2005**, *7*, 2213–2216. (c) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776–5777.
28. (a) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417–2420. (b) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803–805.
29. Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67–70.
30. (a) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547–1550. (b) Witulski, B.; Bushmann, N.; Bergstraber, U. *Tetrahedron* **2000**, *56*, 8473–8480.
31. (a) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663–2666. (b) Mulder, J. A.; Hsung, R. P.; Fredrick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383–1386.
32. (a) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511–2514. (b) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098–2100.
33. (a) Dhimane, A.-L.; Aissa, C.; Malacria, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3284–3287. (b) Fensterbank, L.; Mainetti, E.; Devin, P.; Malacria, M. *Synlett* **2000**, 1342–1344. (c) Devin, P.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1998**, *63*, 6764–6765. (d) Dhimane, A.-L.; Fensterbank, L.; Malacria, M. In Radicals in Organic Synthesis; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 350–382.
34. (a) Blaszykowski, C.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2003**, *5*, 1341–1344. (b) Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 5511–5514.
35. (a) Russel Bowman, W.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747–2762. (b) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009–3018. (c) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765–1768. (d) Curran, D. P.; Liu, H.; Josien, H.; Ko, S.-B. *Tetrahedron* **1996**, *52*, 11385–11404. (e) Boiteau, L.; Boivin, J.; Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1998**, *37*, 1128–1131. (f) Zhou, S.; Bommezijn, S.; Murphy, J. A. *Org. Lett.* **2002**, *4*, 443–445. (g) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3460–3462. (h) Taniguchi, T.; Iwasaki, K.; Uchiyama, M.; Tamura, O.; Ishibashi, H. *Org. Lett.* **2005**, *7*, 4389–4390.
36. For a preliminary communication, see: Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095–5097.
37. Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, 905–910.
38. (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.
39. (a) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1987**, *109*, 2829–2831. (b) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547–2549.
40. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–194.
41. Giraud, L.; Lacôte, E.; Renaud, P. *Helv. Chem. Acta* **1997**, *80*, 2148–2156.
42. Parsons, P. J.; Penverne, M.; Pinto, I. L. *Synlett* **1994**, 721–722.
43. (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834. (b) LLoyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215–236. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16.
44. (a) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104–9105. (b) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511–10520. (c) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305–8314. (d) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869. (e) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627–2635. (f) For reviews, see: Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397–425. (g) Anorbe, L.; Dominguez, G.; Pérez-Castells, J. *Chem. Eur. J.* **2004**, *10*, 4938–4943.
45. (a) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132–2135. (b) Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.;

Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408–3409.
46. Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047–1050.
47. Katritzky, A. R.; Chang, H.-X.; Yang, B. *Synthesis* **1995**, 503–504.
48. Isolation of cyclobutenes from metal catalyzed [2+2] of enynes has been described, see: (a) Pd (II): Trost, B. M.; Yanai, M.; Hoogsten, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294–5295. (b) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636–1638. In the latter case, the double bond is shifted to give a more stable cyclobutene product. (c) Pt(II), see Ref. 44d. (d) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245. (e) Pt(IV): Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1985**, *60*, 5567–5569. In that case, the cyclobutene adduct reacts with O_2. (f) Ga (III): Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294–10295.
49. For a related report of instability, see: Smith, A. B., III; Cui, H. *Org. Lett.* **2003**, *5*, 587–590 and Ref. 48e.
50. (a) Strobel, M. P.; Morin, L.; Paquer, D. *New J. Chem.* **1980**, *4*, 603–608. (b) Mahajan, J. R.; Ferreira, A. L.; Araújo, H. C.; Nunes, B. J. *Synthesis* **1976**, 112–113.
51. Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2005**, *70*, 9345–9353.
52. Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224–232.
53. Nieto-Oberhuber, C.; Lopez, S.; Paz Muñoz, M.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146–6148.
54. The analysis of the crude cycloisomerization product from precursor **54** is consistent with the formation of an *exo*-cyclobutene intermediate.
55. Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431–436.
56. For a preliminary communication, see: Marion, F.; Coulomb, J.; Fensterbank, L.; Courillon, C.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509–1511.