Exploration of ring-closing enyne metathesis for the synthesis of azonino[5,4-*b*]indoles

Daniel Solé,* M.-Lluïsa Bennasar, Tomàs Roca, and Magdalena Valldosera[a]

Dedication

Abstract: The use of the ring-closing enyne metathesis (RCEYM) as a methodology for the synthesis of the azonino[5,4-*b*]indole system, featuring the tricyclic substructure of the alkaloids cleavamine and quebrachamine, has been explored. Three series of enyne substrates were studied for the RCEYM reaction: in addition to the usual substrates bearing either a terminal or an internal alkyne, for the first time enynes with an alkynyl halide moiety were also considered. Although the metathesis cyclization allowed the azoninoindole nucleus to be assembled in all three series, an effective catalytic cycle was only established when using internal alkynes. On the basis of the experimental results, the "yne-then-ene" pathway seems to be the mechanism at play in these reactions.

Introduction

Indolo-fused, medium-sized nitrogen heterocycles are the basic structural units of a variety of natural products. Thus, for example, the azocino[4,3-*b*]indole system is present in the small group of apparicine alkaloids,[1] while a few natural products, such as balasubramide,[2] deoxyisoaustamide,[3] and lundurines,[4] embody an azocine ring 5,4-*b* fused to the indole nucleus. On the other hand, several indole alkaloids belonging to different biogenetic families (e.g., cleavamine,[5] quebrachamine[6] and stemmadenine[7]) are structurally defined by embodying an azonino[5,4-*b*]indole framework (Figure 1).

Over the course of our long-standing interest in natural product synthesis, we have worked towards the development of a unified approach for the construction of bridged indole alkaloids.[8] Thus, using a combination of a ring-closing metathesis (RCM) and a Heck cyclization, we have accomplished the synthesis of several indole alkaloids,[9] including apparicine[10] and cleavamines.[11] We have also recently reported our exploratory studies towards the synthesis of pericine using the sequential RCM-Heck cyclization strategy.[12]

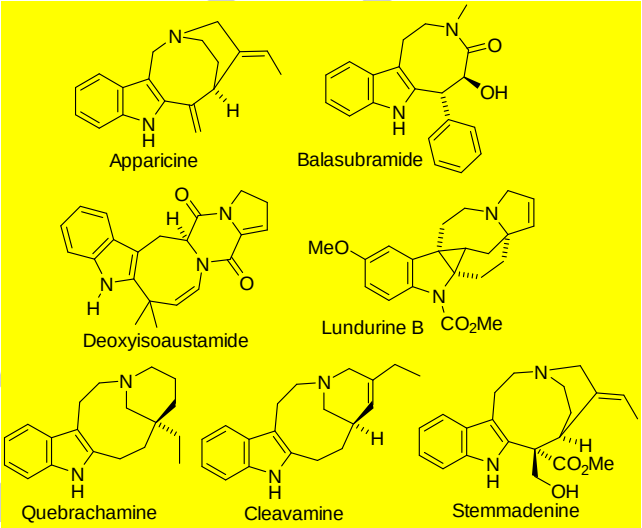
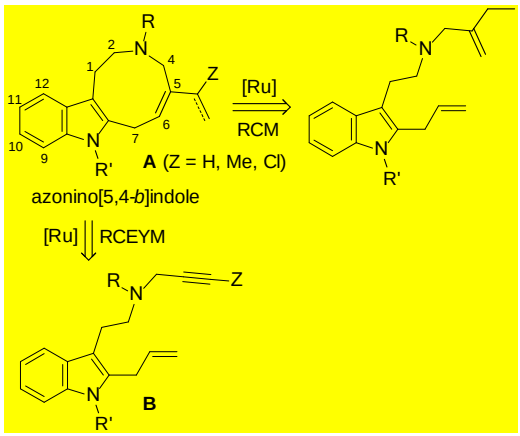


Figure 1. Indole alkaloids with a medium-sized nitrogen heterocycle.

As a continuation of our previous work, we considered applying the ring-closing metathesis strategy for the construction of azonino[5,4-*b*]indoles embodying a C_5-C_6 double bond with an all carbon chain at C_5 (*i.e.* **A**), and featuring the central nine-membered ring present in some alkaloids such as cleavamine[13] and quebrachamine.[14] As depicted in Scheme 1, the assembly of the nine-membered ring would be tackled by two complementary approaches, namely a ring-closing diene metathesis and a ring-closing enyne metathesis (RCEYM).



Scheme 1. Access to the azonino[5,4-*b*]indole **A** by metathesis reactions.

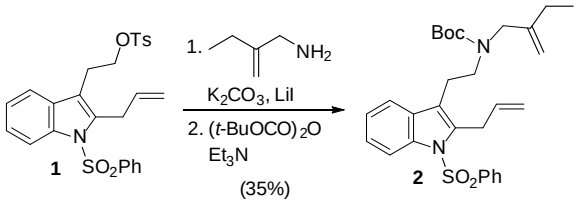
[a] *Prof. Dr. D. Solé, Prof. Dr. M.-L. Bennasar, Dr. T. Roca, M. Valldosera*
Laboratori de Química Orgànica, Facultat de Farmàcia
Universitat de Barcelona
Av. Joan XXIII s/n, 08028 Barcelona, (Spain)
E-mail: dsole@ub.edu
http://www.ub.edu/farmaco/ca/quimica/llistat_recerca

Supporting information for this article is given via a link at the end of the document.

Results and Discussion

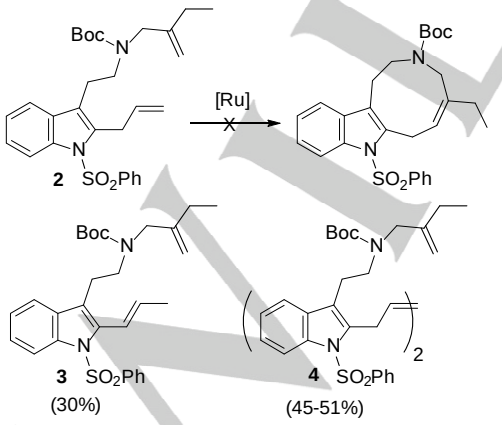
It is widely assumed that medium-sized rings are difficult to access by direct cyclization due to entropic factors and transannular interactions in the transition state. RCM methodologies have proved to be powerful tools to address this issue, being particularly useful in the construction of eight-membered rings.[15] However, the closure of nine-membered rings by RCM can be challenging, most reported successful cyclizations benefiting from some conformational constraints in the substrate.[16]

In the search for an RCM substrate to synthesize the desired azonino[5,4-*b*]indole with the C_5-C_6 double bond and an ethyl substituent at C_5, diene **2** was prepared by alkylation of 2-ethylallylamine[17] with the known tosylate **1**,[9c] followed by protection of the resulting secondary amine with a Boc group (Scheme 2).



Scheme 2. Synthesis of diene **2**.

Unfortunately, exposure of diene **2** to different ruthenium catalysts (second-generation Grubbs catalyst **G2** or second-generation Hoveyda-Grubbs catalyst **H-G2** in CH_2Cl_2 or toluene) did not deliver the expected nine-membered ring. In all assays, only the isomerization product **3** (45-51%) and dimer **4** (≈30%), the latter resulting from an intermolecular metathesis, were obtained (Scheme 3). The failure of the RCM reaction was attributed to the presence of a geminal disubstituted alkene unit in **2**.



Scheme 3. Metathesis of diene **2**.

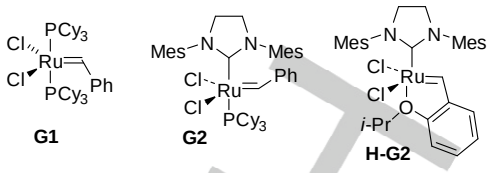
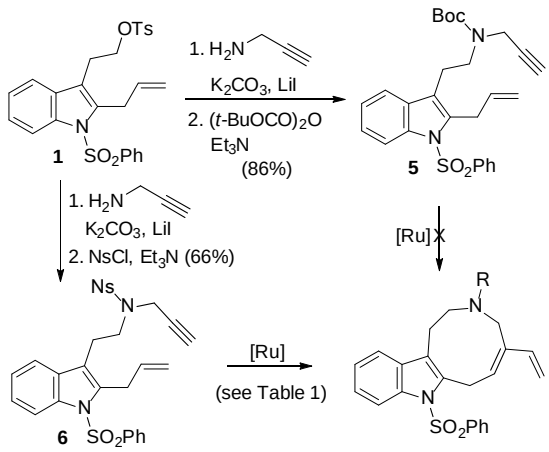


Figure 2. Ru catalysts used in this work.

Considering that in previous studies we had already encountered difficulties in assembling azonino[5,4-*b*]indoles with a trisubstituted double bond functionality using an RCM of dienes,[12] at this point we decided to explore RCEYM reactions instead. The RCEYM is a derivative process of the RCM reaction, consisting of the transition-metal catalyzed skeletal reorganization of one alkene and one alkyne fragment leading to the formation of a cyclic conjugated 1,3-diene.[18] The scope of this powerful and atom-economical transformation has been significantly expanded in recent years to include a host of new applications for the synthesis of cyclic dienes. However, despite its enormous potential, the RCEYM has been scarcely applied to the synthesis of medium-sized rings[19,20] and only isolated examples of nine-membered-ring formation have been reported so far.[21]

To explore the feasibility of assembling the azonino[5,4-*b*]indole system by means of RCEYM reactions, enyne **5** was first examined for its ring closure behavior. Enyne **5** was prepared by alkylation of propargylamine with tosylate **1**, and protection of the resulting secondary amine with a Boc group (Scheme 4). Disappointingly, only extensive decomposition of the substrate was observed when **5** was submitted to the usual RCEYM conditions using ruthenium catalysts **G1** and **G2** in either CH_2Cl_2 or toluene.

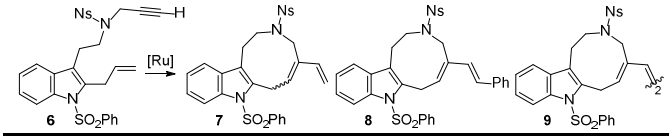
In light of these results, we decided to prepare enyne **6**, which has a *p*-nitrosulfonyl substituent (Nosyl, Ns) at the amine nitrogen, hoping that the more robust protecting group would hamper the extensive decomposition and that the conformational constraint it induces would facilitate the metathetic ring closure. Thus, enyne **6** was prepared from tosylate **1** by reaction with propargylamine, followed by protection with *p*-nitrosulfonyl chloride (Scheme 4).



Scheme 4. Synthesis of enynes **5** and **6** and metathesis reactions.

The most representative results of the RCEYM reactions of enyne **6** are summarized in Table 1. When **6** was subjected to standard RCEYM conditions, involving the use of either the first-generation Grubbs catalyst **G1** (Table 1, entry 1) or the second-generation Grubbs catalyst **G2** (Table 1, entry 2), mainly unchanged material was recovered, although small amounts of azoninoindoles **7*Z***, **7*E***, and **8** were also observed in the reaction mixtures. No significant progression was obtained by extending the reaction times.

Table 1. RCEYM reactions of enyne **6**.[a]



Entry	[Ru] (mol%)	T	*t* [h]	^{1}H NMR ratio	Products [%])[b] (yield
1	**G1** (15)	reflux	23	**6:7*Z*:7*E*:8** (6:1:1:1)	---
2	**G2** (9.5)	r.t.	6	**6:7*Z*:7*E*:8** (8:1:1:1)	---
3	**G2** (22.5)	r.t.	21	**7*Z*:7*E*:8:9** (1:1:1.5:0.5)	---
4	**G2** (50)	r.t.	3	**7*Z*:7*E*:8:9** (1:1:2:0.6)	**7*Z*:7*E*:8** (1:1:4, 35%) **9** (24%)
5	**G2** (17.5)	reflux	30	**7*Z*:7*E*:8:9** (1:1:1:0.5)	**7*E*** (9%) **7*Z*:8** (1:1, 20%) **9** (16%)
6	**H-G2** (12.5)	reflux	24	**7*Z*:7*E*:8'[c]:9** (1:1:1:0.5)	---

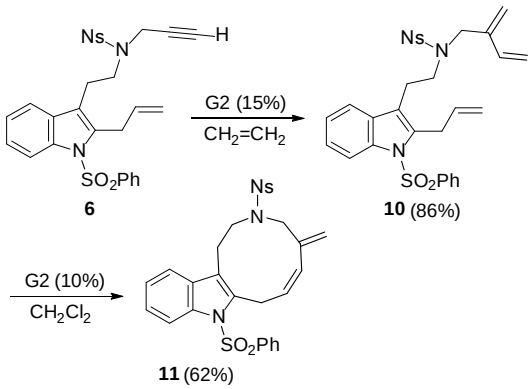
[a] All reactions were performed using a 0.001M solution of **6** in CH_2Cl_2 under an Ar atmosphere. [b] Isolated yields. [c] **8'** is the analog of **8** with an *o*-(*i*-PrO)C_6H_4 group instead of Ph.

In contrast, the starting material was completely consumed when the reaction was run in the presence of a higher amount of **G2** (22.5 mol%) in CH_2Cl_2 at room temperature (Table 1, entry 3). Under these conditions, a 1:1:1.5:0.5 mixture of azoninoindoles **7*Z***, **7*E***, **8**, and **9** was obtained, all of which were derived from the *exo*-mode ring closure pathway. Interestingly, while **7** was obtained as a 1:1 mixture of *Z* and *E* isomers on the endocyclic double bond,[22] only the *Z*-stereochemistry was observed for **8** and **9**, both of which are products of an apparent overreaction of the desired cyclization product **7**. While **8** incorporates a benzylidene substituent proceeding from the precatalyst **G2** on the exocyclic double bond, **9** is the product of metathetic dimerization of **7**.

Increasing the amount of the catalyst **G2** still further enhanced the formation of **8** (Table 1, entry 4). Under these reaction conditions, **7*Z***, **7*E***, **8**, and **9** were obtained as a 1:1:2:0.6 mixture in a combined 59% overall yield. A better ratio of the desired azoninoindoles **7*Z*-7*E*** to the overreaction products **8**-**9** was obtained when using a smaller amount of the catalyst **G2** in CH_2Cl_2 at reflux (Table 1, entry 5). However, after flash chromatography, the cyclization products were isolated in a lower overall yield. The use of the second-generation Hoveyda-Grubbs catalyst **H-G2** afforded a similar result (Table 1, entry 6).

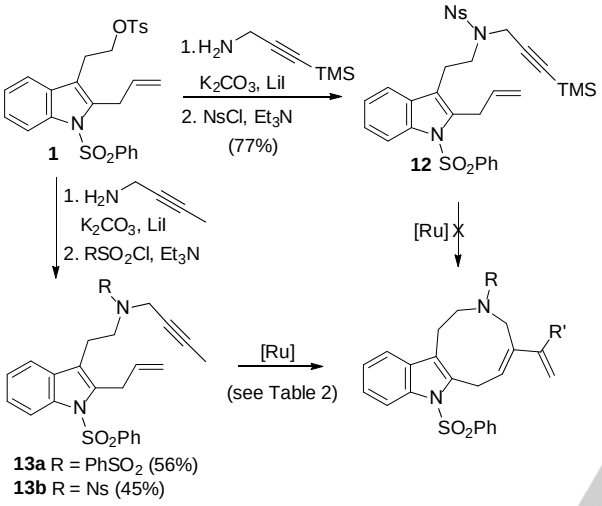
The results summarized in Table 1 suggest that a loss of catalyst metathesis activity occurs during the reactions of enyne **6**, which provide only partial conversion. In consequence, larger amounts of catalyst are required, leading to the formation of the side products **8** and **9**. Experimental and computational studies on the effect of the enyne substituents in RCEYM processes have shown that some competitive non-productive pathways, leading to catalyst deactivation, can take place when the reacting compound is a terminal alkyne.[23]

The beneficial effect of ethylene in the RCEYM reactions of terminal alkynes for the formation of up to 8-membered rings was revealed by the pioneering work of Mori,[24] although the exact nature of this effect is not completely understood.[25] Nevertheless, we suspected that the use of ethylene for the formation of the 9-membered ring of the azonino[5,4-*b*]indole would promote the competitive cross diene metathesis, as occurs in macrocyclization reactions via RCEYM.[26] Indeed, treatment of enyne **6** with catalyst **G2** under an ethylene atmosphere at room temperature produced the cross metathesis product **10** in good yield (Scheme 5). Subsequent RCM of this substrate with **G2** in refluxing CH_2Cl_2 selectively yielded the azecino[5,4-*b*]indole **11**, which otherwise would be the *endo*-product of the RCEYM of **6**. It should be noted that this product was never observed in the RCEYM reaction mixtures of **6** (Table 1), which confirms that the RCEYM selectively follows the *exo*-mode ring closure. These results fully agree with the well established ring size-dependent *exo*/*endo* selectivity in the RCEYM, according to which the formation of common and medium-sized rings generally follows the *exo*-mode ring closure path.[26,27]



Scheme 5. Metathesis of enyne **6** in the presence of ethylene and synthesis of the *endo*-product **11**.

As the use of internal alkynes avoids at least part of the non-productive pathways that occur during the RCEYM reactions leading to medium-sized rings, we decided to explore the metathetic behavior of enynes **12** and **13a-b**, which bear a substituted alkyne moiety. Enynes **12** and **13a-b** were prepared by reaction of tosylate **1** with 3-(trimethylsilyl)-2-propynamine[28] or 2-butynamine, respectively, followed by protection of the resulting secondary amines as the corresponding sulfonamides (Scheme 6).



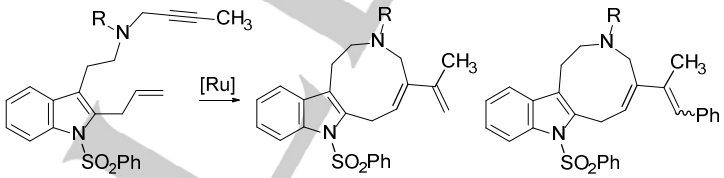
Scheme 6. Synthesis of enynes **12** and **13a-b**, and metathesis reactions.

When **12** was subjected to standard RCM conditions, involving the use of either **G1**, **G2** or **H-G2**, unchanged material was mainly recovered and only small amounts of the corresponding double-bond isomerization product were observed. The low tendency of enyne **12** to undergo RCEYM is probably due to the steric hindrance generated by the bulky TMS group, which hampers the coordination of the alkyne to the ruthenium catalyst required for the metathesis.

We next focused on the reactivity of enynes **13a** and **13b** under RCEYM conditions, hoping that the less bulky methyl group would facilitate the cyclization. The results of these reactions are summarized in Table 2.

Enyne **13a** was less reactive than **6** in the RCEYM reaction and was recovered unchanged when treated with the catalyst **G1** in CH_2Cl_2 at reflux (Table 2, entry 1). Even under forcing conditions, only the starting material was recovered (Table 2, entry 2). The use of **G2** in refluxing CH_2Cl_2 afforded a mixture of the starting material and azoninoindoles **14a** and **15a** (Table 2, entry 3). Changing the solvent to toluene (Table 2, entry 4) or using the catalyst **H-G2** instead of **G2** (Table 2, entry 5) resulted in a slower transformation. More satisfactorily, the material was completely converted when using a higher amount of **G2**, which resulted in the formation of a 3:1 mixture of **14a** and **15a** (Table 2, entry 6). Enyne **13b**, which possesses a *p*-nitrosulfonyl group at the nitrogen atom, showed a similar behavior (Table 2, entry 7). Remarkably, only the *Z*-stereochemistry was observed for the endocyclic double bond of **14a-b** and **15a-b**, which sharply contrasts with the formation of the *Z*- and *E*-isomers in the RCEYM reactions of **6**.

Table 2. RCEYM reactions of enynes **13a-b**.[a]



13a, R = $PhSO_2$ **14a**, R = $PhSO_2$ **15a**, R = $PhSO_2$
13b, R = Ns **14b**, R = Ns **15b**, R = Ns

Entry	Enyne	[Ru] (mol%)	Solvent	T	*t* [h]	^{1}H NMR ratio	Products (yield [%])[b]
1	**13a**	**G1** (10)	CH_2Cl_2	reflux	23		**13a** (95%)
2	**13a**	**G1** (10)	toluene	90 ºC	43		**13a** (63%)
3	**13a**	**G2** (10)	CH_2Cl_2	reflux	67	**13a:14a:15a** (2:3:1)	
4	**13a**	**G2** (10)	toluene	70 ºC	21	**13a:14a:15a** (20:1.5:1)	
5	**13a**	**H-G2** (10)	CH_2Cl_2	reflux	23	**13a:14a:15a'**[c] (32:3:1)	
6	**13a**	**G2** (22.5)	CH_2Cl_2	reflux	47		**14a:15a** (3:1, 52%)
7	**13b**	**G2** (17.5)	CH_2Cl_2	reflux	28		**14a:15a** (4:1, 65%)

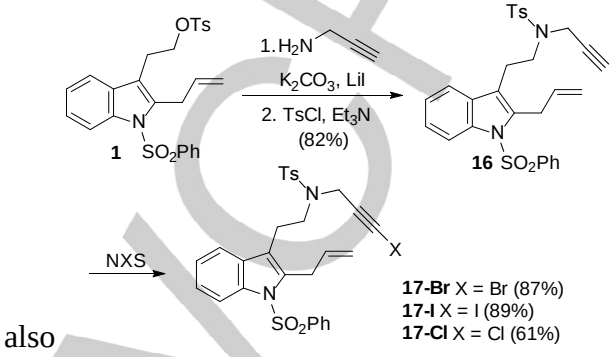
[a] All reactions were performed using a 0.001M solution of the enyne in the indicated solvent under an Ar atmosphere. [b] Isolated yields. [c] **15'** is the analog of

15 with an *o*-(*i*-PrO)C_6H_4 group instead of Ph.

As shown in Table 2, and in agreement with the literature, the internal alkynes **13a-b** afforded much higher ring closing efficiency than the terminal alkyne **6**. From these results we can also conclude that an efficient catalytic cycle is established during the RCEYM of internal enynes **13a-b**.

At this point we decided to explore the use of alkynyl halides in the RCEYM to form the azonino[5,4-*b*]indole system **A** (Scheme 1). Although this usage is unprecedented, we wondered if the application of alkynyl halides[29] in these reactions could benefit from the advantages of internal alkynes while affording a halo-1,3-diene, which would allow further synthetic transformations by transition metal-catalyzed coupling reactions.

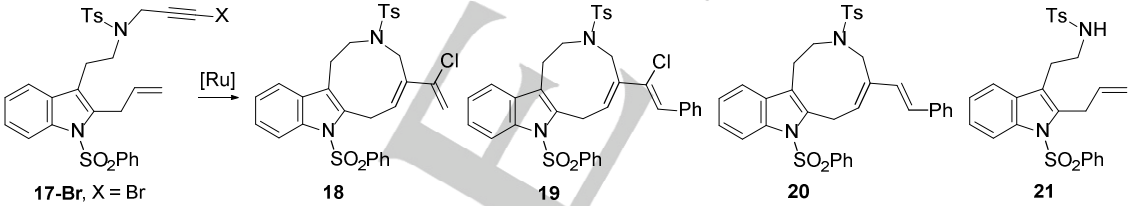
To test the use of alkynyl halides in the RCEYM, we chose enynes **17-Br**, **17-I** and **17-Cl**, which were easily prepared in 71%, 73% and 50% overall yields, respectively, by alkylation of propargylamine with tosylate **1**, followed by protection of the resulting secondary amine with a tosyl group, and halogenation of the terminal alkyne of **16** by reaction with the corresponding *N*-halosuccinimides (Scheme 7).



Scheme 7. Synthesis of haloenynes **17-Br**, **17-I** and **17-Cl**.

With haloenines **17-Br**, **17-I** and **17-Cl** in hand, we focused on their RCEYM reactions (Table 3).

Table 3. RCEYM reactions of enynes **17-Br**, **17-I**, and **17-Cl**.[a]



17-Br, X = Br
17-I, X = I
17-Cl, X = Cl

18 **19** **20** **21**

Entry	Enyne	[Ru] (mol%)	Solvent	T	*t* [h]	^{1}H NMR ratio	Products (yield [%])[b]
1	**17-Br**	**G1** (25)	CH_2Cl_2	reflux	24		**17-Br**
2	**17-Br**	**G2** (15)	CH_2Cl_2	reflux	48	**17-Br:19:21** (10:1:1)	
3	**17-Br**	**G2** (35)	CH_2Cl_2	reflux	71	**18:19:20:21** (1:14:2:2)	**18:19:20** (1:14:2, 35%) **21** (5%)
4	**17-Br**	**G2** (20)	toluene	90 °C	29		---[c]
5	**17-Br**	**H-G2** (15)	CH_2Cl_2	reflux	24		**17-Br**
6	**17-Br**	**G2** (50)	CH_2Cl_2	47 °C[d]	54		**21** (30%)
7	**17-I**	**G2** (35)	CH_2Cl_2	reflux	68	**19:20:21** (10:2:1)	**19:20** (5:1, 35%) **21** (6%)
8	**17-Cl**	**G2** (35)	CH_2Cl_2	reflux	72	**17-Cl:18:19:21** (10:1:10:5.5)	**17-Cl** (21%) **18:19** (1:10, 22%) **21** (10%)

[a] All reactions were performed using a 0.001M solution of the enyne in the indicated solvent, under an Ar atmosphere. [b] Isolated yields. [c] Decomposition, trace amounts of **21** were observed in the reaction mixture. [d] Bath temperature. The reaction was performed under an ethylene atmosphere in a sealed tube.

When **17-Br** was treated with the catalyst **G1** in refluxing CH_2Cl_2, the unchanged starting material was recovered (Table 3, entry 1). Changing the catalyst to **G2** resulted in the formation of small amounts of the dealkylation compound **21** [30] and what seemed to be an azonino[5,4-*b*]indole (Table 3, entry 2). The use of higher amounts of catalyst promoted the complete consumption of the material to give a reaction mixture in which the azonino[5,4-*b*]indole **19** was the major product, although small amounts of the desired cyclization product **18**, the hydrodehalogenation byproduct **20**, and amine **21** were also observed (Table 3, entry 3). After flash chromatography, the three cyclization products were isolated in a modest 35% overall yield. It should be noted that both **18** and **19** bear a Cl substituent instead of the original Br.[31] Interestingly, only the *Z*-stereochemistry was observed for the endocyclic double bond of the cyclization products **18**, **19** and **20**.

Changing the solvent to toluene promoted the decomposition of the material (Table 3, entry 4) and using the catalyst **H-G2** instead of **G2** resulted in no reaction (Table 3, entry 5). On the other hand, treatment of enyne **17-Br** with **G2** under an ethylene atmosphere afforded a complex mixture from which **21** was isolated in 30% yield (Table 3, entry 6).

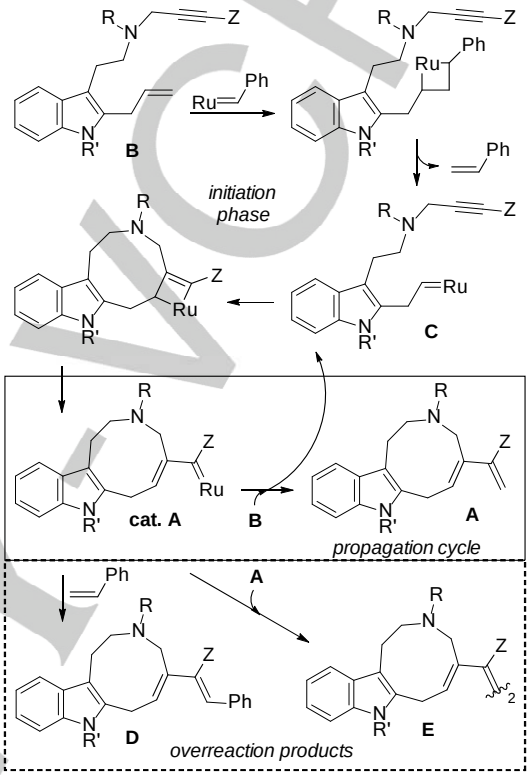
The use of the reaction conditions of entry 3 with alkynyl iodide **17-I** also afforded **19** as the major reaction product, together with minor amounts of **20** and **21** (Table 3, entry 7). Once again, during the metathetic ring closure the iodo substituent was exchanged for Cl. Finally, when the same reaction conditions were used with alkynyl chloride **17-Cl**, although **19** was still the major reaction product, the reaction was comparatively slower and no hydrodehalogenation product was obtained (Table 3, entry 8).

As can be seen in Table 3, the haloenynes **17-Br**, **17-I** and **17-Cl** resemble the terminal enyne **6** in their metathetic behavior, with a similar deactivation of the catalyst during the RCEYM process. Consequently, larger amounts of catalyst are required to achieve the complete conversion of the starting material.

In enyne metathesis, the mechanism at play is still a matter of debate. The question asked is whether an "ene-then-yne" or an "yne-then-ene" pathway is involved.[18] Although most of the experimental data suggest that the "ene-then-yne" mechanism is the most probable when using a Ru-based catalyst,[25,32] experiments presenting evidence in favor of the "yne-then-ene" also exist.[30,33]

The "ene-then-yne" and "yne-then-ene" pathways with the enyne substrates (**B**) studied in our work are shown in Schemes 8 and 9, respectively.

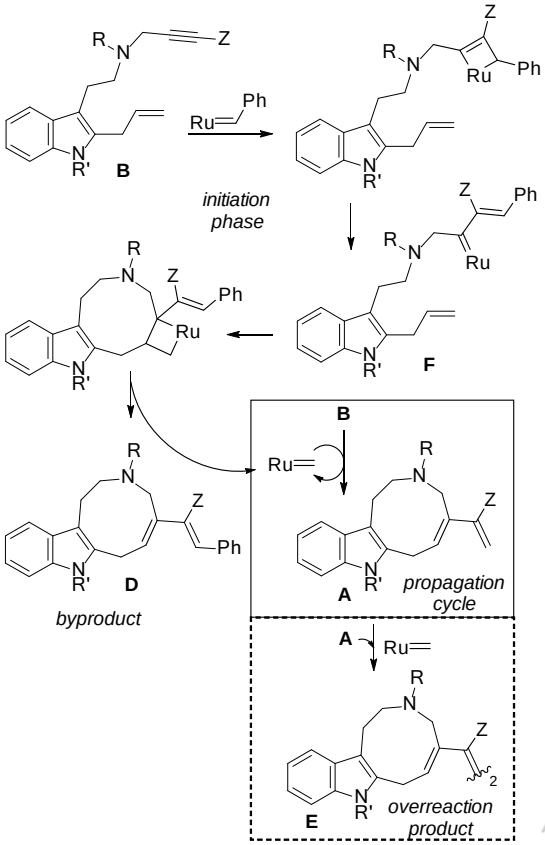
According to the "ene-then-yne" pathway, intermediate **C** would first be formed and a metathesis cyclization would lead to intermediate **cat. A** (Scheme 8). This ruthenium carbene would be the species that reacts with another molecule of enyne **B** through the propagation cycle to give the final product **A**. As the amount of enyne **B** in the reaction mixture is reduced during the RCEYM, **cat. A** would undergo competitive metathetic reactions with vinylbenzene or the cyclization product **A** to give, respectively, **D** or the dimerization product **E**. In consequence, both compounds would actually be overreaction products.



Scheme 8. "Ene-then-yne" pathway with enynes **B**.

On the other hand, following the "yne-then-ene" pathway, intermediate **F** would be generated first (Scheme 9). A subsequent metathesis cyclization would lead to **D**, which should be considered as a reaction byproduct rather than an overreaction product, as well as methylenruthenium, which would be the catalytic species in the propagation cycle of the "yne-then-ene" pathway. Dimer **E** would be formed by cross metathesis overreaction of **A**.

Looking at both reaction mechanisms, it is clear that although both pathways provide the same end product (**A**), the intermediates are very different. Considering the complete initiation of the metathesis catalyst, the most striking difference is that in the "yne-then-ene" pathway, *x* mol% of precatalyst would give rise to *x* mol% of **D**, which bears the benzylidene substituent. In contrast, in the "ene-then-yne" pathway, *x* mol% of vinylbenzene should be obtained.



Scheme 9. "Yne-then-ene" pathway with enynes **B**.

Although all the products obtained in the RCEYM of enynes **6**, **13a-b**, and **17-X** could be a result of either pathway, in our opinion the results of these reactions could be more easily explained by the "yne-then-ene" mechanism. Thus, the ^{1}H NMR analysis of the RCEYM reaction mixtures of terminal alkyne **6** (Table 1) in which low conversion was observed, showed that **8** (**D** in Scheme 9) was present in about 11% (entry 1, Table 1) and 9% (entry 2, Table 1). These percentages are only slightly lower than the amount of precatalyst used in each case. Moreover, the formation of the side product vinylbenzene was not detected in these reaction mixtures.

The same situation was observed in the RCEYM reactions of haloenynes **17-X**. Thus, in the reaction of **17-Br** using 35% of **G2** (entry 3, Table 3), **19** and **20** were obtained in 33% overall yield. Similarly, the RECYM of **17-I** in the presence of 35% of **G2** (entry 7, Table 3) gave **19** and **20** in a combined 35% yield.

Although the situation is less clear in the RCEYM reactions of enynes **13a-b** and the coexistence of both pathways cannot be completely ruled out, we believe that the "yne-then-ene" pathway is still the most likely considering the amount of side products **15a-b** isolated (see entries 6 and 7, Table 2).

Another point at issue of the present RCEYM reactions is why the terminal alkyne **6** gives the cyclization product **7** as a mixture of *Z* and *E* isomers, while only the *Z*-stereochemistry is observed in the side products **8** and **9**, as well as in all the cyclization products of alkynes **13a-b** and haloenynes **17-X**. Although other explanations cannot be excluded,[34] we think that the *Z*/*E* mixture may be due to a secondary metathetical isomerization [26,35] of the initially formed *Z*-stereoisomer.

Conclusions

We have explored the use of the ring-closing enyne metathesis in the synthesis of azonino[5,4-*b*]indoles embodying a C_5-C_6 double bond and an all carbon chain at C_5. Whereas RCEYM of internal alkynes provided an effective route to the azoninoindole nucleus, both terminal alkynes and alkynyl halides failed to establish an efficient catalytic cycle. On the basis of the experimental results, the most likely explanation for the outcome of these RCEYM processes is the "yne-then-ene" mechanism. The RCEYM reactions of alkynyl halides described in this work constitute the first reported study on metathesis cyclizations with this type of alkynes. Further exploration of the use of alkynyl halides in RCEYM reactions for the synthesis of common and medium-sized nitrogen heterocycles, as well as to gain insight into the reaction mechanism, is underway in our laboratory and will be reported in due course.

Experimental Section

General Methods. All commercially available reagents were used without further purification. All nonaqueous reactions were carried out under an argon atmosphere. Reaction courses and product mixtures were routinely monitored by TLC on SiO_2 (silica gel 60 F_{254}), and the spots were located with UV light or 1% aqueous $KMnO_4$ solution. Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure with a rotatory evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04-0.06 mm). ^{1}H- and ^{13}C NMR spectra were recorded in $CDCl_3$ using Me_4Si as the internal standard, with a Varian Gemini 300 or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si for ^{1}H- and ^{13}C NMR. HRMS were obtained using a LC/MSD TOF mass spectrometer.

Synthesis of diene 2

*2-Allyl-3-[2-{N-(2-ethylallyl)-N-(tert-butoxycarbonyl)amino}ethyl]-1-(phenylsulfonyl)indole (**2**).* A mixture of tosylate **1**[9c] (0.68 g, 1.38 mmol), 2-ethylallylamine hydrochloride[15] (1.5 g, 8.28 mmol), K_2CO_3 (1.52 g, 11.04 mmol), and a catalytic amount of LiI in CH_3CN (30 mL) was stirred at 85 °C for 24 h in a sealed tube. The solvent was evaporated and the resulting residue was diluted with CH_2Cl_2 and washed with a saturated aqueous Na_2CO_3 solution. The organic layer was dried, filtered, and concentrated to give the crude secondary amine, which was directly used in the next step. A solution of the secondary amine, Et_3N (0.7 mL, 5.0 mmol), and (*t*-BuOCO)$_2$O (0.51 g, 2.34 mmol) in MeOH (30 mL) was heated at reflux overnight. The solvent was evaporated and the residue was diluted with CH_2Cl_2 and washed with 2N HCl and brine. The organic extracts were dried, filtered, and concentrated to give the crude product. After chromatography (from hexanes to 8:2 hexanes/EtOAc) diene **2** was obtained as a pale yellow oil: 0.25 g (35%); ^{1}H NMR (300 MHz, mixture of rotamers) δ 0.98 (broad q, *J* = 6.9 Hz, 3H), 1.46 and 1.49 (2 s, 9H), 1.90 (m, 2H), 2.82 (m, 2H), 3.24 (m, 2H), 3.47 and 3.69 (2 s, 2H), 3.80

(dt, *J* = 6.0 and 1.5 Hz, 2H), 4.61, 4.69, 4.77 and 4.82 (4 broad signals, 2H), 5.01 and 5.04 (2 s, 2H), 5.98 (m, 1H), 7.25 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.48 (m, 2H), 7.72 (d, *J* = 7.5 Hz, 2H), 8.18 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (100.6 MHz, mixture of rotamers) δ 12.0 and 12.2 (CH_3), 22.8 and 23.4 (CH_2), 26.0 (CH_2), 28.4 and 28.5 (3 CH_3), 30.0 and 30.1 (CH_2), 45.8 and 46.1 (CH_2), 51.7 and 52.6 (CH_2), 79.5 and 79.8 (C), 109.8 and 109.9 (CH_2), 115.0 and 115.1 (CH), 116.1 (CH_2), 118.4 and 118.8 (CH), 119.2 and 119.6 (C), 123.5 and 123.6 (CH), 124.4 (CH), 126.3 (2 CH), 129.1 (2 CH), 130.3 and 130.5 (C), 133.5 (CH), 135.2 and 135.4 (CH), 135.3 (C), 136.6 (C), 139.9 (C), 147.1 and 147.2 (C), 155.3 and 155.5 (C); ESI-HRMS calcd for $C_{29}H_{36}N_2NaO_4S$: 531.2288 $[M+Na]^+$, found: 531.2295.

Characterization data for diene 3 and dimeric compound 4

3-[2-{N-(2-ethylallyl)-N-(tert-butoxycarbonyl)amino}ethyl]-1-(phenylsulfonyl)-2-(propen-1-yl)indole (***3***). Elution with 8:2 hexanes/EtOAc; Yellow oil: ^{1}H NMR (400 MHz, mixture of rotamers) δ 0.97 (broad m, 3H), 1.44 (s, 9H), 1.87 (m, 2H), 1.98 (dd, *J* = 6.4 and 1.6 Hz, 3H), 2.87 (broad signal, 2H), 3.28 (broad signal, 2H), 3.47 and 3.67 (2 broad signals, 2H), 4.57, 4.63, 4.76 and 4.80 (4 broad signals, 2H), 5.75 and 5.80 (2 m, 1H), 6.72 (dd, *J* = 14.0 and 1.6 Hz, 1H), 7.21-7.35 (m, 4H), 7.45 (m, 2H), 7.69 and 7.73 (2 d, *J* = 7.6 Hz, 2H), 8.20 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, mixture of rotamers) δ 12.0 and 12.2 (CH_3), 18.9 (CH_3), 23.5 and 23.9 (CH_2), 26.0 (CH_2), 28.4 (3 CH_3), 45.7 and 46.1 (CH_2), 51.2 and 52.2 (CH_2), 79.5 and 79.7 (C), 109.8 (CH_2), 115.2 (CH), 118.9 and 119.3 (CH), 119.5 (C), 121.1.5 and 121.5 (CH), 123.6 and 123.8 (CH), 124.8 (CH), 126.7 (2 CH), 128.8 (2 CH), 131.2 and 131.5 (C), 132.2 and 132.4 (CH), 133.5 (CH), 135.7 (C), 136.1 (C), 138.6 (C), 147.1 and 147.3 (C), 155.5 (C); ESI-HRMS calcd for $C_{29}H_{36}N_2NaO_4S$: 531.2288 $[M+Na]^+$, found: 531.2292.

Dimer ***4***. Elution with 8:2 hexanes/EtOAc; Yellow oil: ^{1}H NMR (400 MHz, mixture of rotamers) δ 0.96 (t, *J* = 7.6 Hz, 3H), 1.44 (s, 9H), 1.88 (broad signal, 2H), 2.80 (broad signal, 2H), 3.20 (broad signal, 2H), 3.46 and 3.63 (2 broad signals, 2H), 3.69 (broad signal, 2H), 4.61, 4.65, 4.74 and 4.77 (4 broad s, 2H), 5.66 (broad signal, 2H), 7.27 (m, 3H), 7.40 (m, 3H), 7.65 (d, *J* = 5.6 Hz, 2H), 8.14 (d, *J* = 8 Hz, 1H); ^{13}C NMR (100.6 MHz, mixture of rotamers) δ 12.0 and 12.2 (CH_3), 22.7 and 23.4 (CH_2), 26.0 (CH_2), 28.4 (3 CH_3), 28.9 (CH_2), 45.9 and 46.3 (CH_2), 51.8 and 52.3 (CH_2), 79.4 and 79.8 (C), 109.7 (CH_2), 115.2 (CH), 118.4 and 118.9 (CH), 119.0 and 119.4 (C), 123.6 (CH), 124.4 (CH), 126.2 (2 CH), 128.8 (CH), 129.0 (2 CH), 130.4 and 130.6 (C), 133.4 (CH), 135.6 (C), 136.5 (C), 139.0 (C), 147.2 and 147.4 (C), 155.3 and 155.5 (C); ESI-HRMS calcd for $C_{56}H_{68}N_4NaO_8S_2$: 1011.4371 $[M+Na]^+$, found: 1011.4373.

General procedure for the preparation of enynes 5, 6, 12, 13a, and 13 b

A mixture of tosylate **1** (0.50 g, 1.01 mmol), the corresponding propargylic amine (7.07 mmol), K_2CO_3 (0.28 g, 2.02 mmol), and a catalytic amount of LiI in CH_3CN (12 mL) was stirred at 85 °C for 60 h in a sealed tube. The solvent was evaporated and the resulting residue was diluted with CH_2Cl_2 and washed with a saturated aqueous Na_2CO_3 solution. The organic layer was dried, filtered, and concentrated to give the corresponding crude secondary amine, which was directly used in the next step.

A solution of the above amine, Et_3N (0.15 mL, 1.11 mmol), and di-*tert*-butyldicarbonate or the corresponding sulfonylchloride (1.11 mmol) in CH_2Cl_2 (15 mL) was heated at reflux overnight. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed successively with 2N HCl (3 x 25 mL), 2N NaOH (3 x 25 mL), and brine (3 x 25 mL). The organic phase was dried, filtered and concentrated, and the resulting residue was chromatographed (flash, SiO_2) to give the enyne.

Characterization data for enynes 5, 6, 12, 13a, and 13 b

2-Allyl-3-[2-{N-(2-propynyl)-N-(tert-butoxycarbonyl)amino}ethyl]-1-(phenylsulfonyl)indole (***5***). Elution with 8:2 hexanes/AcOEt; Yellow oil: 0.42 g (86%); IR (neat) 3292, 2977, 1693, 1367, 1172 cm^{-1}; ^{1}H NMR (400 MHz, mixture of rotamers) δ 1.48 (s, 9H), 2.19 (broad signal, 1H), 2.94 (t, *J* = 8.4 Hz, 2H), 3.42 (dd, *J* = 7.0 and 6.8 Hz, 2H), 3.72 and 3.96 (2 broad signals, 2H), 3.82 (dt, *J* = 5.6 and 1.6 Hz, 2H), 5.03 (broad signal, 1H), 5.04 (d, *J* = 9.6 Hz, 1H), 6.01 (m, 1H), 7.25 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.60 (broad signal, 1H), 7.71 (d, *J* = 7.6 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz, mixture of rotamers) δ 22.9 and 23.4 (CH_2), 28.3 (3 CH_3), 30.1 (CH_2), 36.4 and 37.5 (CH_2), 46.4 and 46.8 (CH_2), 71.3 and 71.9 (CH), 79.6 (C), 80.4 (C), 115.1 (CH), 116.1 (CH_2), 118.5 (CH), 119.0 (C), 123.6 (CH), 124.4 (CH), 126.2 (2 CH), 129.0 (2 CH), 130.3 (C), 133.5 (CH), 135.3 (CH and C), 136.6 (C), 138.9 (C), 154.7 (C); ESI-HRMS calcd for $C_{27}H_{31}N_2O_4S$: 479.1999 $[M+H]^+$, found: 479.1999.

2-Allyl-3-[2-{N-(2-proynyl)-N-(4-nitrophenylsulfonyl)amino}ethyl]-1-(phenylsulfonyl)indole (***6***). Elution with 2:8 hexanes/CH_2Cl_2; Yellow oil: 0.38 g (66%); IR (neat) 3288, 3104, 1530, 1351, 1166 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.07 (t, *J* = 2.4 Hz, 1H), 2.99 (m, 2H), 3.34 (m, 2H), 3.83 (dt, *J* = 6.0 and 1.6 Hz, 2H), 4.09 (d, *J* = 2.4 Hz, 2H), 5.03 (m, 2H), 6.01 (m, 1H), 7.27 (td, *J* = 7.2 and 1.2 Hz, 1H), 7.32 (td, *J* = 7.2 and 1.2 Hz, 1H), 7.40 (t, *J* = 8.4 Hz, 2H), 7.50 (m, 2H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 24.0 (CH_2), 30.3 (CH_2), 37.3 (CH_2), 46.2 (CH_2), 74.6 (CH), 76.1 (C), 115.2 (CH), 116.3 (CH_2), 117.6 (C), 118.3 (CH), 123.8 (CH), 124.1 (2 CH), 124.7 (CH), 126.4 (2 CH), 128.8 (2 CH), 129.2 (2 CH), 129.8 (C), 133.7 (CH), 135.4 (CH), 135.7 (C), 136.5 (C), 138.9 (C), 144.5 (C), 150.1 (C); ESI-HRMS calcd for $C_{28}H_{26}N_3O_6S_2$: 564.1258 $[M+H]^+$, found: 564.1263.

2-Allyl-3-[2-{N-(4-nitrophenylsulfonyl)-N-(3-trimethylsilyl-2-propynyl)amino}ethyl]-1-(phenylsulfonyl)indole (***12***). Elution with 3:7 hexanes/CH_2Cl_2; Yellow oil: 0.49 g (77%); IR (neat) 2961, 1531, 1448, 1351 cm^{-1}; ^{1}H NMR (400 MHz) δ -0.01 (s, 9H), 3.01 (m, 2H), 3.37 (m, 2H), 3.85 (dt, *J* = 6.0 and 1.6 Hz, 2H), 4.16 (s, 2H), 5.07 (m, 2H), 6.04 (m, 1H), 7.27 (td, *J* = 8.0 and 1.2 Hz, 1H), 7.33 (td, *J* = 8.4 and 2.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.52 (m, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.99 (d, *J* = 9.2 Hz, 2H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (100.6 MHz) δ -0.5 (3 CH_3), 23.8 (CH_2), 30.2 (CH_2), 37.9 (CH_2), 45.8 (CH_2), 91.8 (C), 97.1 (C), 115.1 (CH), 116.3 (CH_2), 117.5 (C), 118.2 (CH), 123.7 (CH), 124.0 (2 CH), 124.6 (CH), 126.3 (2 CH), 128.8 (2 CH), 129.1 (2 CH), 129.8 (C), 133.6 (CH), 135.2 (CH), 135.6 (C), 136.4 (C), 138.8 (C), 144.5 (C), 150.0 (C); ESI-HRMS calcd for $C_{31}H_{34}N_3O_6S_2Si$: 636.1653 $[M+H]^+$, found: 636.1636.

2-Allyl-3-[2-{N-(2-butynyl)-N-(phenylsulfonyl)amino}ethyl]-1-(phenylsulfonyl)indole (***13a***). Elution with 2:8 hexanes/CH_2Cl_2; Yellow oil: 0.30 g (56%); IR (neat) 3066, 2921, 1447, 1364, 1163 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.57 (t, *J* = 2.4 Hz, 3H), 2.98 (m, 2H), 3.30 (m, 2H), 3.84 (dt, *J* = 5.6 and 1.6 Hz, 2H), 4.03 (q, *J* = 2.4 Hz, 2H), 5.06 (m, 2H), 6.03 (m, 1H), 7.29 (m, 2H), 7.39 (t, *J* = 8.4 Hz, 2H), 7.47 (m, 2H), 7.52 (m, 3H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 7.2 Hz, 2H), 8.19 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 3.2 (CH_3), 24.0 (CH_2), 30.2 (CH_2), 37.8 (CH_2), 46.0 (CH_2), 71.7 (C), 81.8 (C), 115.1 (CH), 116.2 (CH_2), 118.2 (C), 118.4 (CH), 123.6 (CH), 124.5 (CH), 126.3 (2 CH), 127.5 (2 CH), 128.7 (2 CH), 129.1 (2 CH), 130.0 (C), 132.5 (CH), 133.6 (CH), 135.3 (CH), 135.5 (C), 136.5 (C), 138.7 (C), 138.9 (C); ESI-HRMS calcd for $C_{29}H_{29}N_2O_4S_2$: 533.1563 $[M+H]^+$, found: 533.1557.

*2-Allyl-3-[2-{N-(2-butynyl)-N-(4-nitrophenylsulfonyl)amino}ethyl]-1-(phenylsulfonyl)indole (**13b**).* Elution with 6:4 hexanes/Et_2O; Yellow oil: 0.26 g (45%); IR (neat) 3104, 2921, 1530, 1350 cm^{-1}; ^1H NMR (400 MHz) δ 1.56 (t, *J* = 2.4 Hz, 3H), 2.97 (m, 2H), 3.31 (m, 2H), 3.83 (dt, *J* = 6.0 and 1.6 Hz, 2H), 4.05 (q, *J* = 2.4 Hz, 2H), 5.04 (m, 2H), 6.02 (m, 1H), 7.26 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.31 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.50 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 8.18 (d, *J* = 7.2 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 3.2 (CH_3), 24.0 (CH_2), 30.2 (CH_2), 37.8 (CH_2), 46.0 (CH_2), 71.4 (C), 82.4 (C), 115.2 (CH), 116.2 (CH_2), 117.7 (C), 118.2 (CH), 123.7 (CH), 123.8 (2 CH), 124.6 (CH), 126.3 (2 CH), 128.8 (2 CH), 129.2 (2 CH), 129.8 (C), 133.6 (CH), 135.4 (CH), 135.6 (C), 136.5 (C), 138.9 (C), 144.7 (C), 150.0 (C); ESI-HRMS calcd for $C_{29}H_{28}N_3O_6S_2$: 578.1414 $[M+H]^+$, found: 578.1414.

General procedure for the preparation of haloenynes 17-Br, 17-I and 17-Cl

*2-Allyl-3-[2-{N-(2-propynyl)-N-(p-toluensulfonyl)amino}ethyl]-1-(phenylsulfonyl)indole (**16**)* was prepared following the general procedure previously described for the preparation of enynes. Elution with 2:8 hexanes/CH_2Cl_2; Yellow oil: 0.44 g (82%); IR (neat) 3286, 2925, 1448, 1348, 1159 cm^{-1}; ^1H NMR (400 MHz) δ 2.14 (t, *J* = 2.8 Hz, 1H), 2.41 (s, 3H), 3.02 (m, 2H), 3.33 (m, 2H), 3.86 (dt, *J* = 5.6 and 1.6 Hz, 2H), 4.08 (d, *J* = 2.8 Hz, 2H), 5.08 (m, 2H), 6.04 (m, 1H), 7.25-7.35 (m, 4H), 7.40 (t, *J* = 8.4 Hz, 2H), 7.53 (m, 2H), 7.70 (d, *J* = 8 Hz, 2H), 7.75 (d, *J* = 8 Hz, 2H), 8.21 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.4 (CH_3), 24.0 (CH_2), 30.1 (CH_2), 37.2 (CH_2), 46.1 (CH_2), 73.8 (CH), 76.8 (C), 115.0 (CH), 116.2 (CH_2), 118.1 (C), 118.4 (CH), 123.6 (CH), 124.4 (CH), 126.2 (2 CH), 127.4 (2 CH), 129.1 (2 CH), 129.4 (2 CH), 129.9 (C), 133.5 (CH), 135.3 (CH), 135.5 (C), 135.6 (C), 136.4 (C), 138.8 (C), 143.6 (C); ESI-HRMS calcd for $C_{29}H_{29}N_2O_4S_2$: 533.1563 $[M+H]^+$, found: 533.1554.

The corresponding succinimide (0.22 mmol) and either $AgNO_3$ (0.02 mmol) or AgOAc (0.02 mmol) were added to a solution of enyne **16** (0.11 g, 0.20 mmol) in acetone (1 mL). After being stirred at rt for 2 h, the reaction mixture was diluted with Et_2O (15 mL) and washed with brine (2 x 15 mL). The organic phase was dried, filtered and concentrated, and the resulting residue was chromatographed (flash, SiO_2) to give enynes **17-X**.

Characterization data for haloenynes 17-Br, 17-I and 17-Cl

*2-Allyl-3-[2-{N-(3-bromo-2-proynyl)-N-(p-toluensulfonyl)}aminoethyl]-1-(phenylsulfonyl)indole (**17-Br**)*. Elution with 1:9 hexanes/CH_2Cl_2. Yellow oil: 106 mg (87%); IR (neat) 3065, 2926, 1448, 1348, 1160 cm^{-1}; ^1H NMR (400 MHz) δ 2.39 (s, 3H), 2.95 (m, 2H), 3.25 (m, 2H), 3.82 (dt, *J* = 6.0 and 1.6 Hz, 2H), 4.02 (s, 2H), 5.03 (m, 2H), 6.02 (m, 1H), 7.25-7.32 (m, 4H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.50 (m, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 8.18 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 24.1 (CH_2), 30.2 (CH_2), 38.5 (CH_2), 45.4 (C), 46.3 (CH_2), 73.2 (C), 115.2 (CH), 116.3 (CH_2), 118.1 (C), 118.5 (CH), 123.8 (CH), 124.6 (CH), 126.3 (2 CH), 127.6 (2 CH), 129.2 (2 CH), 129.6 (2 CH), 130.0 (C), 133.7 (CH), 135.4 (CH and C), 135.6 (C), 136.6 (C), 138.9 (C), 143.8 (C); ESI-HRMS calcd for $C_{29}H_{28}BrN_2O_4S_2$: 611.0668 $[M+H]^+$, found: 611.0671.

*2-Allyl-3-[N-(3-iodo-2-proynyl)-N-tosyl-2-aminoethyl]-1-(phenylsulfonyl)indole (**17-I**)*. Elution with 1:9 hexanes/CH_2Cl_2. Yellow oil: 117 mg (89%); IR (neat) 2925, 1448, 1347, 1159 cm^{-1}; ^1H NMR (400 MHz) δ 2.40 (s, 3H), 2.95 (m, 2H), 3.26 (m, 2H), 3.81 (d, *J* = 6.0 Hz, 2H), 4.14 (s, 2H), 5.03 (m, 2H), 6.02 (m, 1H), 7.25-7.32 (m, 4H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.49 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 8.19 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 2.2 (C), 21.5 (CH_3), 24.0 (CH_2), 30.2 (CH_2), 39.2 (CH_2), 46.3 (CH_2), 87.0 (C), 115.1 (CH), 116.3 (CH_2), 118.1 (C), 118.5 (CH), 123.8 (CH), 124.5 (CH), 126.3 (2 CH), 127.6 (2 CH), 129.1 (2 CH), 129.6 (2 CH), 130.0 (C), 133.6 (CH), 135.3 (CH and C), 135.6 (C), 136.5 (C), 138.9 (C), 143.7 (C); ESI-HRMS calcd for $C_{29}H_{28}IN_2O_4S_2$: 659.053 $[M+H]^+$, found: 659.0531.

*2-Allyl-3-[N-(3-chloro-2-proynyl)-N-tosyl-2-aminoethyl]-1-(phenylsulfonyl)indole (**17-Cl**)*. Elution with 1:9 hexanes/CH_2Cl_2. Yellow oil: 69 mg (61%); IR (neat) 3065, 2926, 1448, 1349, 1160 cm^{-1}; ^1H NMR (400 MHz) δ 2.39 (s, 3H), 2.95 (m, 2H), 3.25 (m, 2H), 3.82 (dt, *J* = 5.6 and 1.6 Hz, 2H), 4.00 (s, 2H), 5.02 (m, 2H), 6.01 (m, 1H), 7.25-7.32 (m, 4H), 7.38 (t, *J* = 8.4 Hz, 2H), 7.49 (m, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 24.2 (CH_2), 30.3 (CH_2), 37.8 (CH_2), 46.3 (CH_2), 62.7 (C), 63.7 (C), 115.2 (CH), 116.2 (CH_2), 118.2 (C), 118.4 (CH), 123.8 (CH), 124.6 (CH), 126.3 (2 CH), 127.5 (2 CH), 129.2 (2 CH), 129.6 (2 CH), 130.0 (C), 133.7 (CH), 135.4 (CH and C), 135.6 (C), 136.6 (C), 138.9 (C), 143.8 (C); ESI-HRMS calcd for $C_{29}H_{28}ClN_2O_4S_2$: 567.1174 $[M+H]^+$, found: 567.1185.

General procedure for the RCEYM reactions

A solution of the corresponding enyne (0.10 mmol) and the Ru catalyst (7.5 mol%) in the indicated solvent (110 mL) was stirred at reflux under Ar. Additional portions of the catalyst were added at regular intervals (12 h) until completion of the reaction by TLC (see Tables 1-3). The reaction mixture was concentrated, and the resulting residue was chromatographed (flash, SiO_2).

Characterization data for 7*Z*, 7*E*, 8, 8', and 9

*(E)-3-(4-Nitrophenylsulfonyl)-8-(phenylsulfonyl)-5-(vinyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**7E**)*. ***7E*** was isolated as a colorless oil (9%) from the crude reaction mixture corresponding to entry 5 of Table 1; IR (neat) 3105, 2927, 1531, 1446, cm^{-1}; ^1H NMR (400 MHz, assignment aided by HSQC and COSY ^1H-^1H) δ 2.70 (m, 1H, H-1), 2.75 (m, 1H, H-2), 2.99 (ddd, *J* = 15.6, 9.6, and 6.0 Hz, 1H, H-1), 3.25 (d, *J* = 11.6 Hz, 1H, H-4), 3.84 (ddd, *J* = 15.2, 10.0, and 4.8 Hz, 1H, H-2). 3.99 (dd, *J* = 16.4 and 12 Hz, 1H, H-7), 4.27 (dd, *J* = 16.4 and 4.8 Hz, 1H, H-7), 4.75 (d, *J* = 11.2 Hz, 1H, H-4), 5.37 (d, *J* = 10.4 Hz, 1H, CH_2=), 5.74 (d, *J* = 17.2 Hz, 1H, CH_2=), 5.78 (dd, *J* = 11.2 and 4.8 Hz, 1H, H-6), 6.60 (dd, *J* = 17.6 and 11.2 Hz, 1H, CH=), 7.24 (td, *J* = 7.6 and 1.2 Hz, 1H, H-11), 7.30 (td, *J* = 7.6 and 1.6 Hz, 1H, H-10), 7.33 (d, *J* = 7.6 Hz, 1H, H-12), 7.41 (t, *J* = 7.6 Hz, 2H, Ph), 7.54 (t, *J* = 8.0 Hz, 1H, Ph), 7.70 (d, *J* = 7.2 Hz, 2H, Ph), 7.96 (d, *J* = 8.8 Hz, 2H, Ph), 8.18 (d, *J* = 8.4 Hz, 1H, H-9), 8.34 (d, *J* = 8.8 Hz, 2H, Ph); ^{13}C NMR (100.6 MHz) δ 25.8 (CH_2, C-1), 26.9 (CH_2, C-7), 48.9 (CH_2, C-2), 53.3 (CH_2, C-4), 115.2 (CH, C-9), 117.7 (CH, C-12), 118.3 (CH_2, CH_2=), 123.2 (C, C-12b), 123.8 (CH, C-11), 124.5 (2 CH, Ph), 125.0 (CH, C-10), 126.2 (2 CH, Ph), 128.1 (2CH, Ph), 129.3 (2 CH, Ph), 130.9 (C, C-12a), 131.0 (CH, CH=), 133.4 (C, C-5), 133.7 (C, Ph), 133.9 (CH and C, C-6 and Ph), 136.3 (C, C-8a), 138.8 (C, C-7a), 144.7 (C, Ph), 150.0 (C, Ph); ESI-HRMS calcd for $C_{28}H_{26}N_3O_6S_2$: 564.1258 $[M+H]^+$, found: 564.1256.

*(Z)-3-(4-Nitrophenylsulfonyl)-8-(phenylsulfonyl)-5-(vinyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**7Z**) and 3-(4-Nitrophenylsulfonyl)-8-(phenylsulfonyl)-5-(2-phenylvinyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**8**)*. A *1:1 mixture of **7Z** and **8*** was obtained (20% overall combined yield) from the crude reaction mixture corresponding to entry 5 of Table 1. ^1H NMR (400 MHz, assignment aided by HSQC) δ 2.96 (m, 4H, ***7Z*****/8**), 3.48 (t, *J* = 6.0 Hz, 2H, ***7Z***), 3.55 (t, *J* = 6.0 Hz, 2H, **8**), 3.93 (d, *J* = 7.6 Hz, 2H, ***7Z***), 3.95 (s, 2H, ***7Z***), 3.97 (d, *J* = 8.2 Hz, 2H, **8**), 4.10 (s, 2H, **8**), 5.06 (d, *J* = 11.2 Hz, 1H, ***7Z***), 5.24 (d, *J* = 17.6 Hz, 1H, ***7Z***), 6.20 (t, *J* = 7.6 Hz, 1H, ***7Z***), 6.30 (t, *J* = 8.2 Hz, 1H, **8**), 6.34 (dd, *J* = 17.6 and

11.2 Hz, 1H, ***7Z***), 6.58 (d, *J* = 16.4 Hz, 1H, **8**), 6.70 (d, *J* = 16.4 Hz, 1H, **8**), 7.20-7.40 (m, 15H, ***7Z***/**8**), 7.50 (m, 2H, ***7Z***/**8**), 7.72 (m, 4H, ***7Z***/**8**), 7.77 and 7.81 (2d, *J* = 8.8 Hz, 4H, ***7Z***/**8**), 8.07 (t, *J* = 8.4 Hz, 2H, ***7Z***/**8**), 8.17 and 8.21 (2d, *J* = 8.8 Hz, 4H, ***7Z***/**8**); ^{13}C NMR (100.6 MHz, assignment aided by HSQC, aromatic signals are not assigned) δ 22.8 (CH_2, **8**), 23.0 (CH_2, ***7Z***), 25.3 (CH_2, ***7Z***), 25.5 (CH_2, **8**), 44.3 (CH_2, ***7Z***), 44.5 (CH_2, **8**), 48.2 (CH_2, **8**), 48.4 (CH_2, ***7Z***), 112.9 (CH_2, ***7Z***), 114.9 (CH), 117.8 (CH), 117.9 (CH), 117.9 (C), 118.0 (C), 123.6 (CH), 123.7 (CH), 124.0 (CH), 124.1 (CH), 124.7 (CH), 124.8 (CH), 126.2 (CH), 126.3 (CH), 127.7 (CH), 128.0 (CH, **8**), 128.3 (CH), 128.4 (CH), 128.7 (CH), 129.0 (C), 129.3 (CH), 130.7 (CH, **8**), 132.4 (C), 133.8 (CH, ***7Z***/**8**), 134.0 (C, **8**), 134.1 (C, ***7Z***), 135.0 (C), 136.0 (C), 136.9 (C), 138.8 (C), 138.9 (CH, ***7Z***), 144.5 (C), 144.7 (C), 149.8 (C); ESI-HRMS calcd for $C_{28}H_{26}N_3O_6S_2$: 564.1258 (***7Z***, $[M+H]^+$), found: 564.1251; ESI-HRMS calcd for $C_{34}H_{30}N_3O_6S_2$: 640.1571 (**8**, $[M+H]^+$), found: 640.1559.

5-[2-(2-isopropoxyphenyl)vinyl]-3-(4-nitrophenylsulfonyl)-8-(phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole **8'**. Signals from a *1:1 mixture of **7Z** and **8'*** obtained from the crude reaction mixture corresponding to entry 6 of Table 1 (20% overall combined yield). ^{1}H NMR (400 MHz, aromatic signals are not shown) δ 1.34 (d, *J* = 5.6 Hz, 6H), 2.97 (m, 2H), 3.49 (m, 2H), 4.01 (d, *J* = 8.0 Hz, 2H), 4.09 (s, 2H), 4.55 (h, *J* = 5.6 Hz, 1H), 6.26 (t, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 16.4 Hz, 1H), 6.98 (d, *J* = 16.4 Hz, 1H), 6.46 (s, 1H).

*Dimer **9*** was isolated as a yellow oil (16%) from the crude reaction mixture corresponding to entry 5 of Table 1; IR (neat) 3027, 1606, 1530, 1448, cm^{-1}; ^{1}H NMR (400 MHz, assignment aided by HSQC) δ 3.01 (t, *J* = 6.0 Hz, 4H), 3.48 (t, *J* = 6.0 Hz, 4H), 3.85 (s, 4H); 3.95 (d, *J* = 7.6 Hz, 4H), 6.20 (t, *J* = 7.6 Hz, 2H), 6.22 (s, 2H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.26 (m, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 4H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 4H), 7.81 (d, *J* = 9.2 Hz, 4H), 8.05 (d, *J* = 8.4 Hz, 2H), 8.20 (d, *J* = 8.4 Hz, 4H); ^{13}C NMR (100.6 MHz) δ 23.5 (CH_2), 25.4 (CH_2), 45.3 (CH_2), 48.6 (CH_2), 114.9 (CH), 117.7 (C), 117.9 (CH), 123.7 (CH), 124.2 (2 CH), 124.8 (CH), 126.3 (2 CH), 128.4 (2 CH), 128.8 (C), 129.4 (2 CH), 130.2 (CH), 132.4 (CH), 133.8 (CH), 134.0 (C), 135.2 (C), 136.1 (C), 138.8 (C), 144.1 (C), 149.9 (C); ESI-HRMS calcd for $C_{54}H_{50}N_7O_{12}S_4$: 1116.2394 $[M+NH_4]^+$, found: 1116.2370.

Metathesis reaction of 6 under ethylene

*2-Allyl-3-[2-{N-(2-methylen-3-butenyl)-N-(4-nitrophenylsulfonyl)amino}ethyl]-1-(phenylsulfonyl)indole (**10**)*. A solution of enyne **6** (53 mg, 0.09 mmol) and the catalyst **G2** (12 mg, 15 mol%) in CH_2Cl_2 (100 mL) was stirred at rt under ethylene for 3 h. The reaction mixture was concentrated and the resulting residue was chromatographed (3:7 hexanes/CH_2Cl_2) to give **10** as a brown oil: 43 mg (86%)**;** IR (neat) 2925, 1531, 1349, 1164 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.92 (m, 2H), 3.11 (m, 2H), 3.76 (d, *J* = 5.6 Hz, 2H), 4.00 (s, 2H), 4.95 (dq, *J* = 16.8 and 1.2 Hz, 1H), 5.01 (dq, *J* = 10.4 and 0.8 Hz, 1H), 5.09 (s, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 5.28 (s, 1H), 5.55 (d, *J* = 17.6 Hz, 1H), 5.98 (m, 1H), 6.38 (dd, *J* = 18.0 and 11.2 Hz, 1H), 7.28 (m, 2H), 7.38 (t, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 7.6 Hz, 1H), 8.32 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 25.2 (CH_2), 30.1 (CH_2), 47.6 (CH_2), 51.1 (CH_2), 115.1 (CH), 116.1 (CH_2), 116.7 (CH_2), 117.9 (C), 118.3 (CH), 119.7 (CH_2), 123.7 (CH), 124.4 (2 CH), 124.6 (CH), 126.4 (2 CH), 128.3 (2 CH), 129.1 (2 CH), 129.8 (C), 133.6 (CH), 135.4 (C), 135.5 (CH), 135.6 (CH), 136.5 (C), 138.9 (C), 140.4 (C), 144.6 (C), 150.0 (C); ESI-HRMS calcd for $C_{30}H_{29}N_3NaO_6S_2$: 614.1390 $[M+Na]^+$, found: 614.1400.

RCM of triene 10

*5-Methylene-3-(4-nitrophenylsulfonyl)-9-(phenylsulfonyl)-2,3,4,8-tetrahydro-1(H)-azecino[5,4-b]indole (**11**)*. A solution of triene **10** (35 mg, 0.06 mmol) and the catalyst **G2** (5 mg, 10 mol%) in CH_2Cl_2 (60 mL) was stirred at reflux overnight. The reaction mixture was concentrated and the resulting residue was chromatographed (3:7 hexanes/AcOEt) to give **11** as a yellow oil: 21 mg (62%)**;** IR (neat) 3025, 2917, 1530, 1448, 1349 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.95 (t, *J* = 5.2 Hz, 2H), 3.58 (t, *J* = 4.8 Hz, 2H), 3.78 (d, *J* = 7.6 Hz, 2H), 4.24 (br s, 2H), 5.05 (s, 1H), 5.37 (s, 1H), 6.16 (d, *J* = 11.2 Hz, 1H), 6.39 (dt, *J* = 11.2 and 8.0 Hz, 1H), 7.04 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.09 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.14 (td, *J* = 8.0 and 1.6 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.50 (m, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 23.9 (CH_2), 24.0 (CH_2), 50.7 (CH_2), 55.0 (CH_2), 114.7 (CH), 115.4 (CH_2), 115.9 (C), 117.7 (CH), 123.0 (2 CH), 123.3 (CH), 124.4 (CH), 126.2 (2 CH), 128.4 (2 CH), 128.8 (C), 129.3 (2 CH), 131.3 (CH), 131.7 (CH), 133.7 (CH), 135.7 (C), 137.5 (C), 139.1 (C), 143.6 (C), 144.7 (C), 149.2 (C); ESI-HRMS calcd for $C_{28}H_{26}N_3O_6S_2$: 564.1258 $[M+H]^+$, found: 564.1254.

Characterization data for 14a, 14b, 15a, and 15b

*5-(1-Methylvinyl)-3,8-di(phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**14a**)*. An analytical sample of **14a** was obtained by additional flash chromatography of a 3:1 mixture of **14a**/**15a** (entry 6, Table 2); Yellow oil: IR (neat) 3022, 2926, 1446, 1361 cm^{-1}; ^{1}H NMR (400 MHz, assignment aided by HSQC) δ 1.85 (d, *J* = 0.8 Hz, 3H), 2.83 (t, *J* = 6.0 Hz, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 4.01 (s, 2H), 4.07 (d, *J* = 8.4 Hz, 2H), 4.94 (s, 1H), 5.01 (s, 1H), 6.15 (t, *J* = 8.4 Hz, 1H), 7.21 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.27 (td, *J* = 8.4 and 1.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.51 (m, 3H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100.6 MHz, assignment aided by HSQC) δ 21.6 (CH_3), 22.3 (CH_2), 25.3 (CH_2), 45.3 (CH_2), 47.7 (CH_2), 113.0 (CH_2), 114.9 (CH), 117.9 (CH), 119.7 (C), 123.5 (CH), 124.6 (CH), 126.2 (2 CH), 127.4 (2 CH), 128.0 (CH), 129.1 (2 CH), 129.3 (2 C), 129.5 (C), 132.7 (CH), 133.7 (CH), 134.1 (C), 135.6 (C), 136.1 (C), 138.6 (C), 139.1 (C), 142.8 (C); ESI-HRMS calcd for $C_{29}H_{29}N_2O_4S_2$: 533.1563 $[M+H]^+$, found: 533.1560.

*5-(1-Methyl-2-phenylvinyl)-3,8-(diphenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**15a,** mixture of Z/E isomers on the exocyclic double bond)*. Signals from a 3:1 mixture of **14a**/**15a** (entry 6, Table 2). ^{1}H NMR (400 MHz, assignment aided by HSQC, aromatic signals are not shown) δ 1.93 (d, *J* = 1.2 Hz, 3H major isomer), 2.92 (t, *J* = 6.0 Hz, 2H major isomer), 2.98 (t, *J* = 6.0 Hz, 2H minor isomer), 3.41 (t, *J* = 6.0 Hz, 2H major isomer), 3.54 (t, *J* = 6.0 Hz, 2H minor isomer), 4.03 (s, 2H major isomer), 4.12 (d, *J* = 8.4 Hz, 2H major isomer), 5.62 (t, *J* = 8.4 Hz, 1H minor), 6.22 (t, *J* = 8.4 Hz, 1H major isomer), 6.48 (s, 1H major isomer), 6.59 (s, 1H minor isomer); ^{13}C NMR (100.6 MHz, assignment aided by HSQC, aromatic signals and quaternary carbons are not shown) δ 21.6 (CH_3), 22.4 (CH_2), 25.4 (CH_2), 45.8 (CH_2), 47.7 (CH_2), 127.2 (CH), 128.2 (CH); ESI-HRMS calcd for $C_{35}H_{33}N_2O_4S_2$: 609.1876 $[M+H]^+$, found: 609.1863.

*5-(1-Methylvinyl)-3-(4-nitrophenylsulfonyl)-8-(phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**14b**)*. An analytical sample of **14b** was obtained by additional flash chromatography of a 4:1 mixture of **14b**/**15b** (entry 7, Table 2); Yellow oil: IR (neat) 2925, 1530, 1448, 1348 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.88 (s, 3H), 2.89 (t, *J* = 6.0 Hz, 2H), 3.43 (t, *J* = 6.0 Hz, 2H), 4.00 (d, *J* = 8.0 Hz, 2H), 4.09 (s, 2H), 4.98 (s, 1H), 5.04 (s, 1H), 6.21 (t, *J* = 8.0 Hz, 1H), 7.21 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.31 (m, 2H), 7.39 (t, *J* = 8.4 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 21.6 (CH_3), 22.5 (CH_2), 25.5 (CH_2), 45.0 (CH_2), 47.7 (CH_2), 113.0 (CH_2), 114.9 (CH), 117.8 (CH), 118.6 (C), 123.6

(CH), 124.2 (2 CH), 124.7 (CH), 126.2 (2 CH), 128.4 (2 CH), 128.7 (CH), 129.1 (C), 129.3 (2 CH), 133.8 (CH), 134.1 (C), 135.7 (C), 136.0 (C), 139.0 (C), 142.9 (C), 144.5 (C), 149.9 (C); ESI-HRMS calcd for $C_{29}H_{28}N_3O_6S_2$: 578.1414 $[M+H]^+$, found: 578.1413.

*5-(1-Methyl-2-phenylvinyl)-3-(4-nitrophenylsulfonyl)-8-(phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**15b,** mixture of Z/E isomers on the exocyclic double bond).* Signals from a 4:1 mixture of **14b**/**15b** (entry 7, Table 2). ^{1}H NMR (400 MHz, aromatic signals are not shown) δ 1.94 (d, *J* = 1.2 Hz, 3H major isomer), 2.97 (t, *J* = 6.0 Hz, 2H major isomer), 3.49 (t, *J* = 6.0 Hz, 2H major isomer), 4.00 (d, *J* = 8.2 Hz, 2H major isomer), 4.21 (s, 2H major isomer), 6.27 (t, *J* = 8.2 Hz, 1H major isomer), 6.46 (s, 1H major isomer); ESI-HRMS calcd for $C_{35}H_{32}N_3O_6S_2$: 654.1727 $[M+H]^+$, found: 654.1713.

Characterization data for 18, 19, 20, and 21

*5-(1-Chlorovinyl)-3-(p-toluensulfonyl)-8-(phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**18**).* From a 1:10 mixture of **18**/**19** (entry 8, Table 3): ^{1}H NMR (400 MHz, assignment aided by HSQC, aromatic protons are not shown) δ 2.42 (s, 3H), 2.86 (t, *J* = 6.0 Hz, 2H), 3.34 (t, *J* = 6.0 Hz, 2H), 3.92 (s, 2H), 4.09 (d, *J* = 7.8 Hz, 2H), 5.36 (d, *J* = 2.0 Hz, 1H), 5.52 (d, *J* = 2.0 Hz, 1H), 6.60 (t, *J* = 7.8 Hz, 1H). ESI-HRMS calcd for $C_{29}H_{28}ClN_2O_4S_2$: 567.1174 $[M+H]^+$, found: 567.1206.

*5-(1-Chloro-2-phenylvinyl)-3-(p-toluensulfonyl)-8-(phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**19**).* From a 1:10 mixture of **18**/**19** (entry 8, Table 3): ^{1}H NMR (400 MHz, assignment aided by HSQC) δ 2.39 (s, 3H), 2.95 (t, *J* = 6.0 Hz, 2H), 3.37 (t, *J* = 6.0 Hz, 2H), 4.00 (s, 2H), 4.17 (d, *J* = 7.8 Hz, 2H), 6.60 (t, *J* = 7.8 Hz, 1H), 6.82 (s, 1H), 7.23-7.43 (m, 10H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 7.6 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 22.9 (CH_2), 25.3 (CH_2), 46.3 (CH_2), 48.3 (CH_2), 114.9 (CH), 117.9 (CH), 119.6 (C), 123.5 (CH), 124.7 (CH), 126.3 (2 CH), 126.5 (CH), 127.4 (2 CH), 128.0 (CH), 128.1 (2 CH), 129.3 (2 CH and C), 129.6 (2 CH), 129.8 (2 CH), 131.7 (CH), 132.6 (C), 133.3 (C), 133.7 (CH), 135.0 (C), 135.1 (C), 135.3 (C), 136.2 (C), 139.0 (C), 143.7 (C); ESI-HRMS calcd for $C_{35}H_{32}ClN_2O_4S_2$: 643.1487 $[M+H]^+$, found: 643.1491.

*(E)-5-(2-phenylvinyl)-3-(p-toluensulfonyl)-8-(phenylsulfonyl)-2,3,4,7-tetrahydro-1(H)-azonino[5,4-b]indole (**20**).* From a 1:14:2 mixture of **18**/**19**/**20** (entry 3, Table 3); ^{1}H NMR (400 MHz, assignment aided by HSQC, aromatic protons are not shown) δ 2.43 (s, 3H), 2.94 (t, *J* = 5.6 Hz, 2H), 3.40 (t, *J* = 5.6 Hz, 2H), 3.96 (s, 2H), 4.11 (d, *J* = 8.2 Hz, 2H), 6.22 (t, *J* = 8.2 Hz, 1H), 6.45 (d, *J* = 16.4 Hz, 1H), 6.65 (d, *J* = 16.4 Hz, 1H); ESI-HRMS calcd for $C_{35}H_{36}N_3O_4S_2$: 626.2141 $[M+NH_4]^+$, found: 626.2136.

*2-Allyl-3-[2-{N-(p-toluensulfonyl)amino}ethyl]-1-(phenylsulfonyl)indole (**21**).* Yellow oil: IR (neat) 3305, 2929, 1945, 1598, 1447 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.39 (s, 3H), 2.83 (t, *J* = 6.8 Hz, 2H), 3.75 (q, *J* = 6.8 Hz, 2H), 3.75 (dt, *J* = 6.0 and 1.2 Hz, 2H), 4.27 (t, *J* = 6.4 Hz, 1H), 4.94 (dq, *J* = 17.2 and 1.2 Hz, 1H), 5.01 (dq, *J* = 9.6 and 1.6 Hz, 1H), 5.96 (m, 1H), 7.20 (m, 3H), 7.29 (m, 2H), 7.40 (t, *J* = 8.4 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 25.0 (CH_2), 30.2 (CH_2), 42.3 (CH_2), 115.2 (CH), 116.4 (CH_2), 117.8 (C), 118.3 (CH), 123.7 (CH), 124.6 (CH), 126.3 (2 CH), 126.9 (2 CH), 129.2 (2 CH), 129.6 (2 CH), 129.7 (C), 133.7 (CH), 135.5 (CH), 135.8 (C), 136.6 (C), 136.7 (C), 138.8 (C), 143.5 (C); ESI-HRMS calcd for $C_{26}H_{27}N_2O_4S_2$: 495.1407 $[M+H]^+$, found: 495.1409.

Acknowledgements

The authors gratefully acknowledge financial suppor for this work from the Spanish Ministerio de Economía y Competitividad, Fondos Europeos para el Desarrollo Regional (MINECO-FEDER) (grant number CTQ2012-31391).

Keywords: Ring-closing enyne metathesis • ruthenium • cyclization • medium-sized heterocycles • nine-membered ring

[1] a) B. Gilbert, A. P. Duarte, Y. Nakagawa, J. A. Joule, S. E. Flores, J. A. Brissolese, J. Campello, E. P. Carrazzoni, R. J. Owellen, E. C. Blossey, K. S. Brown Jr., C. Djerassi, *Tetrahedron* **1965**, *21*, 1141. b) J. A. Joule, H. Monteiro, L. J. Durham, B. Gilbert, C. Djerassi, *J. Chem. Soc.* **1965**, 4773.

[2] B. Riemer, O. Hofer, H. Greger, *Phytochemistry* **1997**, *45*, 337.

[3] P. S. Steyn, *Tetrahedron* **1973**, *29*, 107.

[4] T.-S. Kam, K. Yoganathan, C.-H. Chuah, *Tetrahedron Lett.* **1995**, *36*, 759.

[5] a) G. A. Cordell in *Indoles, The Monoterpenoid Indole Alkaloids*, Vol. 25, (Ed.: J. E. Saxton), Wiley: New York, **1983**, Part 4, Chapter 10. b) J. E. Saxton in *Monoterpenoid Indole Alkaloids*, Supplement to Vol. 25, (Ed.: J. E. Saxton), Wiley: Chichester, **1994**, Part 4, Chapter 10.

[6] a) J. E. Saxton in *Indoles, The Monoterpenoid Indole Alkaloids*, Vol. 25, (Ed.: J. E. Saxton), Wiley: New York, **1983**, Part 4, Chapter 8. b) J. E. Saxton in *Monoterpenoid Indole Alkaloids*, Supplement to Vol. 25, (Ed.: J. E., Saxton), Wiley: Chichester, **1994**, Part 4, Chapter 8.

[7] A. I. Scott, C.-L. Yen, D. Greenslade, *J. Chem. Soc., Chem. Commun*. **1978**, 947-948.

[8] For a review, see: M.-L. Bennasar in *Targets in Heterocyclic Systems. Chemistry and Properties*, *Vol. 17* (Eds.: O. A. Attanasi, D. Spinelli), Società Chimica Italiana, Roma, Italy, **2013**, pp. 35-56.

[9] a) M.-L. Bennasar, E. Zulaica, D. Solé, S. Alonso, *Synlett* **2008**, 667. b) M.-L. Bennasar, E. Zulaica, D. Solé, S. Alonso, *Tetrahedron* **2012**, *68*, 4641. c) M.-L. Bennasar, D. Solé, E. Zulaica, S. Alonso, *Tetrahedron* **2013**, *69*, 2534.

[10] a) M.-L. Bennasar, E. Zulaica, D. Solé, S. Alonso, *Chem. Commun.* **2009**, 3372. b) M.-L. Bennasar, E. Zulaica, D. Solé, T. Roca, D. García-Díaz, S. Alonso, *J. Org. Chem.* **2009**, *74*, 8359.

[11] M.-L. Bennasar, D. Solé, E. Zulaica, S. Alonso, *Org. Lett.* **2011**, *13*, 2042.

[12] M.-L. Bennasar, D. Solé, T. Roca, M. Valldosera, *Tetrahedron* **2015**, *71*, 2246.

[13] For recent synthesis of cleavamines, see: M. Amat, C. Escolano, O. Lozano, N. Llor, J. Bosch, *Org. Lett.* **2003**, *5*, 3139. See also reference 11.

[14] For recent synthesis of quebrachamine, see: a) H. K. Grover, M. A. Kerr, *Synlett* **2015**, 815. b) S.-W. Hsu, H.-Y. Cheng, A.-C. Huang, T.-L. Ho, D.-R. Hou, *Eur. J. Org. Chem.* **2014**, 3109. c) J. E. Nidhiry, K. R. Prasad, *Tetrahedron* **2013**, *69*, 5525. d) B. Bajtos, B. L. Pagenkopf, *Eur. J. Org. Chem.* **2009**, 1072. e) E. S. Sattely, S. J. Meek, S. J. Malcolmson, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 943.

[15] For specific reviews, see: a) M. E. Maier, *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. b) L. Yet, *Chem. Rev.* **2000**, *100*, 2963. c) A. Michaut, J. Rodriguez, *Angew. Chem., Int. Ed.* **2006**, *45*, 5740. d) N. Blanchard, J. Eustache, in *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*, (Eds.: J. Cossy, S. Arseniyadis, C. Meyer), Wiley-VCH, Weinheim, Germany, **2010**; pp. 1-43. e) M. Tori, R. Mizutani, *Molecules* **2010**, *15*, 4242.

[16] For the synthesis of azonine rings by RCM, see: a) M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. Hii, P. N. Horton, M. B. Hursthouse, *J. Org. Chem.* **2005**, *70*, 1552. b) R. Kaul, S.

Surprenant, W. D. Lubell, *J. Org. Chem.* **2005**, *70*, 3838. c) D. Enders, A. Lenzen, M. Backes, C. Janeck, K. Catlin, M.-I. Lannou, J. Runsink, G. Raabe, *J. Org. Chem.* **2005**, *70*, 10538.

[17] M.-L. Bennasar, T. Roca, D. García-Díaz, *J. Org. Chem.* **2008**, *73*, 9033.

[18] For reviews, see: a) C. S.Poulsen, R. Madsen, *Synthesis* **2003**, 1. b) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317. c) S. T. Diver, *J. Mol. Catal. A* **2006**, *254*, 29. d) H. Villar, M. Frings, C. Bolm, *Chem. Soc. Rev.* **2007**, *36*, 55. e) S. T. Diver, *Coord. Chem. Rev.* **2007**, *251*, 671. f) M. Mori, *Adv. Synth. Catal.* **2007**, *349*, 121.

[19] For the synthesis of 7-membered rings, see: a) J. S. Clark, G. P. Trevitt, D. Boyall, B. Stammen, *Chem. Commun.,* **1998**, 2629. b) J. S. Clark, F. Elustondo, G. P. Trevitt, D. Boyall, J. Robertson, A. J. Blake, C. Wilson, B. Stammen, *Tetrahedron*, **2002**, *58*, 1973. c) J. S. Clark, F. Elustondo, M. C. Kimber, *Chem. Commun.,* **2004**, 2470. d) M. A. Evans, J. P. Morken, *Org. Lett.* **2005**, *7*, 3371. e) K. C. Majundar, H. Rahaman, R. Islam, B. Roy, *Tetrahedron Lett.* **2006**, *47*, 2111. f) D. A. Kummer, J. B. Brenneman, S. F. Martin, *Tetrahedron*, **2006**, *62*, 11437. g) F.-D. Boyer, I. Hanna, *Org. Lett.* **2007**, *9*, 715. h) J. S. Harvey, G. T. Giuffredi, V. Gouverneur, *Org. Lett.* **2010**, *12*, 1236. i) K. C. Majundar, *RSC Adv.,* **2011**, *1*, 1152. j) L.-L. Zhang, W.-Z. Zhang, X. Ren, X.-Y. Tan, X.-B. Lu, *Tetrahedron Lett.* **2012**, *53*, 3389.

[20] For the synthesis of 8-membered rings, see: a) M. Mori, T. Kitamura, N. Sakakibara, Y. Sato, *Org. Lett.* **2000**, *2*, 543. b) E. Groaz, D. Banti, M. North, *Adv. Synth. Catal.* **2007**, *349*, 142. c) E. Comer, E. Rohan, L. Deng, J. A. Porco Jr., *Org. Lett.* **2007**, *9*, 2123.

[21] a) M. Mori, T. Kitamura, Y. Sato, *Synthesis* **2001**, 654. b) M. Lejkowski, P. Benerjee, S. Schüller, A. Münch, J. Runsink, C. Vermeeren, H.-J. Gais, *Chem. Eur. J.* **2015**, *18*, 3529.

[22] Some spectroscopic features clearly differentiate **7*Z*** and **7*E*** (see experimental section). While the two protons of each methylene (C_1, C_2, C_4 and C_7) of the nine-membered ring of **7*Z*** are equal due to its high conformational flexibility, the highly rigid and twisted structure of **7*E*** makes these protons diastereotopic.

[23] See, for example: F. Nuñez-Zarur, X. Solans-Monfort, L. Rodríguez-Santiago, M. Sodupe, *ACS Catal.* **2013**, *3*, 206; and references therein.

[24] M. Mori, N. Sakikabara, A. Kinoshita, *J. Org. Chem.* **1998**, *63*, 6082.

[25] a) G. C. Lloyd-Jones, R. G. Margue, J. G. de Vries, *Angew. Chem. Int. Ed.* **2005**, *44*, 7442. b) A. G. D. Grotevendt, J. A. M. Lummiss, M. L. Mastronardi, D. E. Fogg, *J. Am. Chem. Soc.* **2011**, *133*, 15918.

[26] E. C. Hansen, D. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 15074.

[27] E. C. Hansen, D. Lee, *J. Am. Chem. Soc.* **2003**, *125*, 9582.

[28] J. Egger, C. Weckerle, B. Cutting, O. Schwardt, S. Rabbani, K. Lemme, B. Ernst, *J. Am. Chem. Soc.* **2013**, *135*, 9820.

[29] For the use of vinyl and alkynyl halides in Pt-catalyzed cycloisomerization reactions, see: N. Chatani, N. Furukawa, H. Sakurai, S. Murai, *Organometallics* **1996**, *15*, 901.

[30] For the formation of dealkylation products in RCEYM reactions, see: N. Dieltiens, K. Moonen, C. V. Stevens, *Chem. Eur. J.* **2007**, *13*, 203.

[31] A closely related exchange, in which the original halide is replaced by a chloride from the ruthenium catalyst, has been observed in diene RCM reactions starting from vinyl halides: M. L. Macnaughtan, J. B. Gary, D. L. Gerlach, M. J. A. Johnson, J. W. Kampf, *Organometallics* **2009**, *28*, 2880.

[32] a) T. R. Hoye, S. M. Donaldson, T. J. Vos, *Org. Lett.* **1999**, **1**, 277. b) J. J. Lippstreu, B. F. Straub, *J. Am. Chem. Soc.* **2005**, *127*, 7444.

[33] a) A. Kinoshita, M. Mori, *Synlett* **1994**, 1020. b) E. Vedrenne, F. Royer, J. Oble, L. E. Kaïm, L. Grimaud, *Synlett* **2005**, 2379. c) B. R. Galan, A. J. Giessert, J. B. Keister, S. T. Diver, *J. Am. Chem. Soc.* **2005**, *127*, 5762. d) H. Clavier, A. Correa, E. C. Escudero-Adán, J. Benet-Buchholz, L. Cavallo, S. P. Nolan, *Chem. Eur. J.* **2009**, *15*, 10244.

[34] As suggested by one of the referees, a mixture of **7*Z*** and **7*E*** could be directly formed in the propagation cycle starting from **6**. If so, the selective formation of the *Z* stereochemistry for the overreaction product 9 might be the result of a stereochemical discrimination during the diene cross metathesis overreaction, which would be faster from the more accessible **7*Z*** isomer than from **7*E***.

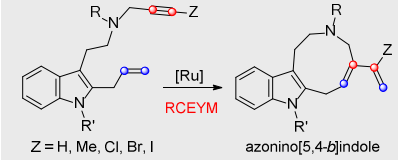
[35] W. C. Lee, R. H. Grubbs, *Org. Lett.* **2000**, *2*, 2145.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Ring-closing enyne metathesis: The use of RCEYM as a methodology for the construction of the nine-membered ring of the 2,3,4,7-tetrahydro-1(*H*)-azonino[5,4-*b*]indole system has been explored



Key Topic*: Ring-closing enyne metathesis

Daniel Solé, M.-Lluïsa Bennasar, Tomàs Roca, and Magdalena Valldosera*[a]

Page No. – Page No.

Exploration of ring-closing enyne metathesis for the synthesis of azonino[5,4-*b*]indoles