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Ring-Closing Metathesis Reactions of Bis(enynes): Selectivity and Surprises

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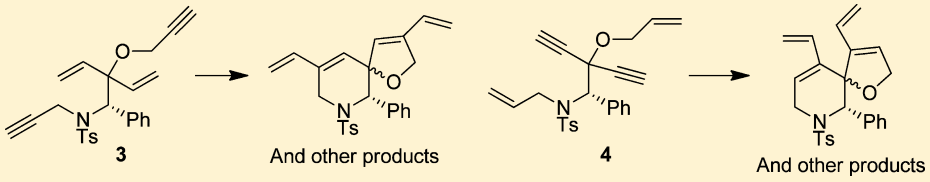
Supporting Information



ABSTRACT: A study of the ring-closing metathesis reactions of two bis(enynes) is presented. These substrates, which contain two alkenes and two alkynes, as well as a resident stereocenter, can potentially generate metathesis products resulting from many reaction pathways. In this contribution we present our results on these reactions, show how small changes in reaction conditions can lead to different product ratios, and attempt to provide a rationale for the outcomes.

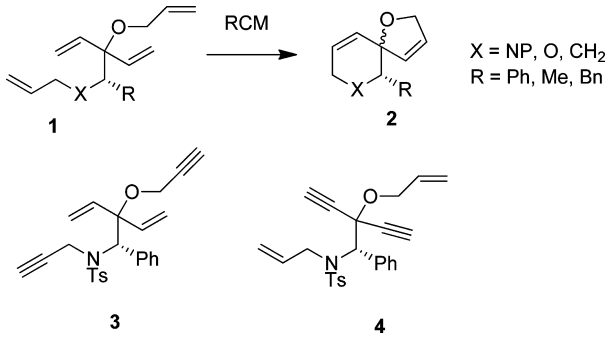
INTRODUCTION

Over the past two decades the ruthenium-mediated ring-closing metathesis reaction has become one of the most widely used synthetic transformations in organic chemistry, and many groups have successfully incorporated such reactions into the synthesis of natural and unnatural products.[1] In some cases the careful design of starting materials has allowed for multiple rings to be formed in a single synthetic step from acylic starting materials.[2−4] The ability to generate more than one ring has found particular success when employing enyne metathesis;[5] in these substrates the first ring-closing event generates a new ruthenium vinyl carbene which is available for further reaction with other carbon multiple bonds within the molecule.[6] For example, in dienyne metathesis[7] reaction of the intermediate ruthenium vinyl carbene with a second olefin leads to a fused bicyclic structure in a cascade-type process. In contrast, multiple ring-closing reactions of alkenes rely on two discrete ring-closing events, each requiring an intermolecular reaction between catalyst and substrate. Previously our group has explored the double ring-closing metathesis of tetraenes such as **1**, which lead to spirocyclic molecules of general structure **2** via two separate ring-closing steps (Scheme 1).[8] As part of our continuing interest in this area the ring-closing metathesis reactions of bis(enynes) **3** and **4** were considered. These substrates, which contain two alkenes and two alkynes, can potentially generate metathesis products resulting from many reaction pathways. In this contribution we present our results on ring-closing metathesis reactions of these compounds, show how small changes in reactions conditions can lead to different product ratios, and attempt to provide a rationale for the outcomes.

RESULTS AND DISCUSSION

Synthesis of Substrates. Compound **3** was prepared in 71% yield from the previously described **5**[8b] by reaction with sodium hydride and propargyl bromide. Compound **4** was prepared in two steps from **6** by reaction with propargylmagnesium bromide to give **7**, followed by allylation with allyl bromide and sodium hydroxide. This final step was hindered by formation of a rearrangement byproduct **8**, which predominated when employing sodium hydride as base. After screening a number of different conditions the use of sodium hydroxide in DMF[9] was found to be optimum, giving a 2:1 ratio of **4**:**8** and allowing for isolation of 57% of **4** after chromatography (Scheme 2).

Scheme 1. Bis(enynes) for Ring-Closing Metathesis Study



Ring-Closing Metathesis of 3. Initial studies were conducted using **3** and a typical "second-generation" catalyst, **9**.[10] Reaction of a dichloromethane solution of **3** with 20 mol % **9** gave, after 3 h, two major products in a 1:2 ratio, along with a number of minor components.[11] After separation these were confirmed to be spirocyclic compounds **10a** and **10b** formed in 50% combined yield (Scheme 3). NMR studies allowed for assignment of the major isomer as **10b**, based on an NOE

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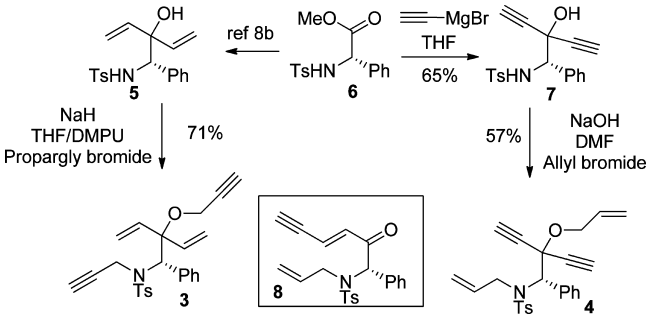
Scheme 2. Synthesis of 3 and 4



between the aromatic ortho proton and the olefinic proton in the 5-membered ring, which was lacking in **10a**. A number of the minor reaction components showed incorporation of the aromatic portion of the catalyst moiety, suggesting incomplete turnover of initially generated alkenes. Repeating the reaction under an ethylene atmosphere gave a cleaner reaction profile; **10a** and **10b** were isolated in 74% yield, again in a 1:2 ratio. We propose this reaction proceeds by initial reaction of the catalyst with one of the alkyne moieties followed by cyclization onto a hindered vinyl group to afford **11a** and **b** or **12a** and **b**. A second intermolecular event is then required between catalyst and the remaining alkyne to initiate the second ring closure. The relative contribution of these two pathways to the reaction outcome has not been determined as no significant quantities of the putative monocyclic intermediates **11** or **12** were detected under the reaction conditions. In an attempt to stall the reaction at these intermediates a reduced catalyst load was used (4 mol % of **9**). In this case incomplete conversion was seen, but the only products detected were once again **10a** and **10b**, with 70% of starting material recovered. This result suggests that formation of the first ring is the rate-determining step, and the monocyclic intermediates are rapidly consumed in a fast second step, explaining their nondetection.

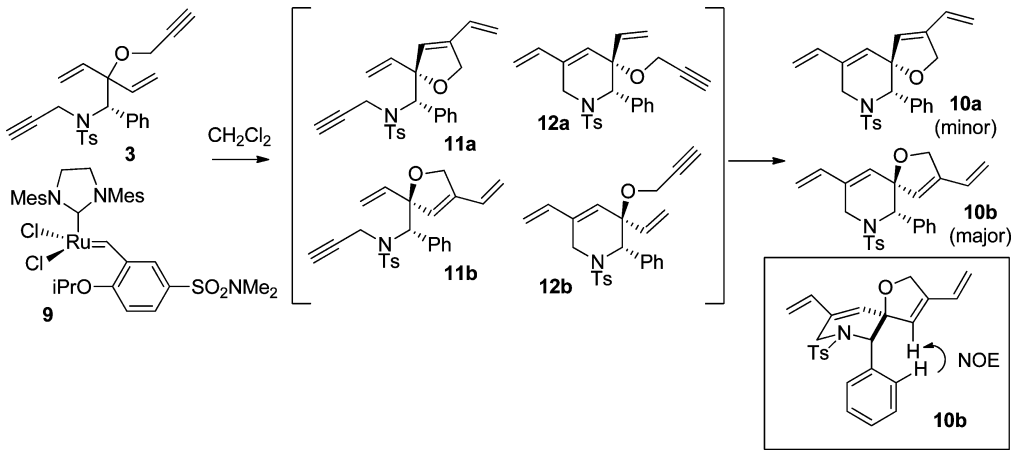
Reaction of **3** with a typical "first-generation" catalyst, **13**[12] was then evaluated. In the absence of ethylene 30% conversion to one major product was seen, along with several minor components. On the basis of real-time HPLC analysis an intermediate was initially generated which subsequently converted to final product; notably, neither the intermediate nor product had been seen in reactions of **3** with catalyst **9**. After isolation the major product was found to be a single stereoisomer of tricycle **14**, presumably resulting from an intramolecular Diels–Alder reaction between the diene and alkyne moieties in either **11** or **12**. Intermolecular Diels–Alder reactions of dienes formed in an enyne metathesis reaction with an external dienophile have been extensively reported,[13] and intramolecular variants following enyne cross metathesis reactions are also known;[14] however, instances where both the metathesis and the Diels–Alder steps are intramolecular are less common,[15] and to the best of our knowledge this is the first example where the sequence occurs in a single step. NOE studies showed the vinyl group, the central methine proton, and the benzylic proton were all cis to each other, allowing for assignment of stereochemistry as shown (Scheme 4).

Attempts to isolate the transient intermediate **11** or **12**, or trap with an external dienophile were unsucessful due to the rapid conversion to the intramolecular Diels–Alder product. Notably product **14** could arise from *either* a six- or five-membered ring intermediate, but only from one stereoisomer of each, i.e. from **11b** or **12a**.

Carrying out the ring-closing reaction of **3** with **13** under an ethylene atmosphere allowed for complete conversion of starting material and reduced the number of minor byproducts. After 3 h the same intermediate as previously was seen, this was subsequently consumed to give four products. Two were the known spirocycles **10a** and **10b** in a 1:2 ratio, accounting for about 30% of the total mixture. The balance of material was split equally between the Diels–Alder product **14** and a second new product, determined to be cyclopropane **15** (Scheme 5). The stereochemistry in **15** was determined on the basis of a number of NOE experiments. First the cyclopropane group was shown to be "back" based on an NOE between the cyclopropane methylene and the olefin as shown. Unambiguous assignment of the quaternary center was more challenging due lack of diagnostic NOEs between the 5- and 6-membered rings; however, an NOE between the aromatic ortho-protons and the cyclopropane methine allowed for final assignment as shown.

Formation of the cyclopropane is interesting from a mechanistic standpoint. Although cyclopropanes are often observed as minor byproducts in metathesis reactions due to catalyst decomposition,[16,17] in this case the quantities generated are in excess of the catalyst loading. A catalytic tandem cyclopropanation/dienyne metathesis has been previously reported and is thought to result from interplay of catalyst decomposition through a reductive elimination pathway and a

Scheme 3. Ring-Closing Metathesis of 3 Promoted by 9



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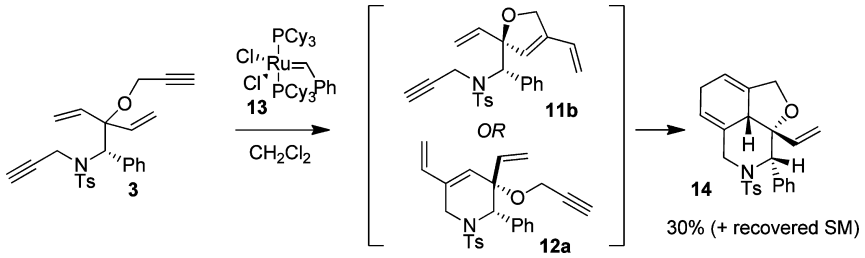
Scheme 4. Ring-Closing Metathesis and Diels-Alder Reaction of 3 Promoted by 13



Scheme 5. Ring-Closing Metathesis of 3 Promoted by 13 under an Ethylene Atmosphere

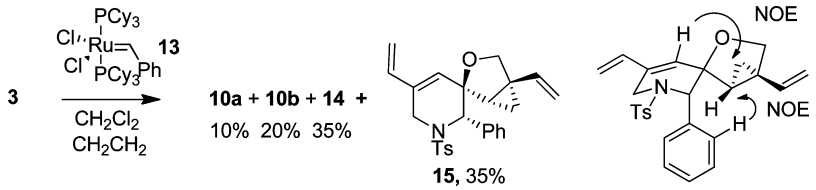
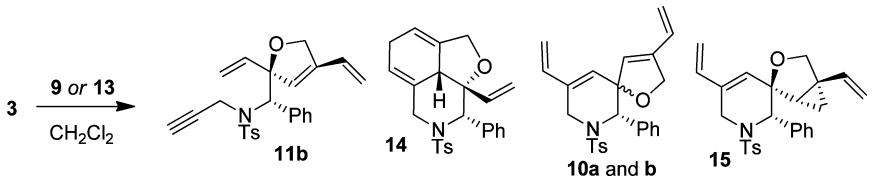


Table 1. Summary of Ring-Closing Metathesis Products from 3



conditions	conversion (%)	**11b**	**14**	**10a** and **10b** all ~1:2 ratio	**15**
12 h, 20 mol % **9**	60	–	–	60	–
12 h, 20 mol % **9**, C_2H_4	100	–	–	98	2
3 h, 20 mol % **13**	25	19	6	–	–
24 h, 20 mol %**13**	41	2	38	~1	~1
2 h, 20 mol % **13**, C_2H_4	71	43	16	5	7
18h, 20 mol % **13**, C_2H_4	100	9	30	25	34
6 h, 10 mol % **13**, C_2H_4	90	39	29	10	12
48 h, 10 mol% **13**, C_2H_4	100	0	54	22	24
2h, 5 mol%**13**, C_2H_4	62	36	18	3	4
48 h, 5 mol % **13**, C_2H_4	90	0	61	12	17

noncarbenic enyne bond reorganization.[18] As such an enyne starting material is required to both generate the cyclopropane and give pathways to allow metal carbene regeneration; indeed we confirmed that resubmission of **10a** or **10b** to the reaction conditions (catalyst **13** and ethylene) did not generate any cyclopropane. Compound **15** appears to be formed from the same intermediate that generates the Diels–Alder product[19] and based on the stereochemistry in **14** and **15** the intermediate is thought to be **11b**. Certainly, initial formation of a 5-membered ring would be favored on kinetic grounds and was observed in our previous work on tetraenes.[8d,e] Moreover formation of **11b** could account for formation of all products other than **10a**—which constitutes <10% of the final mixture.

The study of ring-closing metathesis reactions of **3** have shown that, when using a reactive catalyst (such as **9**) spirocyclic compounds resulting from a double enyne metathesis are formed, with a modest degree of stereoselection. When using a less reactive catalyst such as **13** the second enyne ring closure is slowed sufficiently for other processes to compete, leading to cyclopropane and Diels–Alder products as well as the spirocycles.[20] As the catalyst load is reduced, cyclopropanation is also inhibited, and the Diels–Alder product becomes the major constituent in up to 61% yield (Table 1).

Ring Closing Metathesis of 4. Attention then switched to reaction of bis(enyne) **4**. Reaction with catalyst **9** under an ethylene atmosphere led to conversion to five compounds of which the major component accounting for 40% of the mixture[11] was the spirocycle **16a** resulting from a double enyne metathesis reaction. Interestingly, essentially a single stereoisomer was formed[21] and was assigned as **16a** on the basis of lack of significant NOE interactions between the aromatic group and the vinyl group of the 5-membered ring which would have been expected for **16b**.[22] The other four compounds, accounting for the remaining 60% of the reaction mixture, were found to be the fused bicyclic compounds **17a**, **17b**, **18a**, and **18b** which are the expected products of dienyne-type cyclization. Such products had not been observed during reactions of **3** due to steric constraints but in this case are clearly competitive with the spirocycle formation. Reaction of **4** promoted by **9** in the absence of ethylene afforded the same five products, but in this case the spirocycle **16a** only accounted for 15% of the mixture and dienyne products for 85%. Moreover the relative ratios of the dienyne products were

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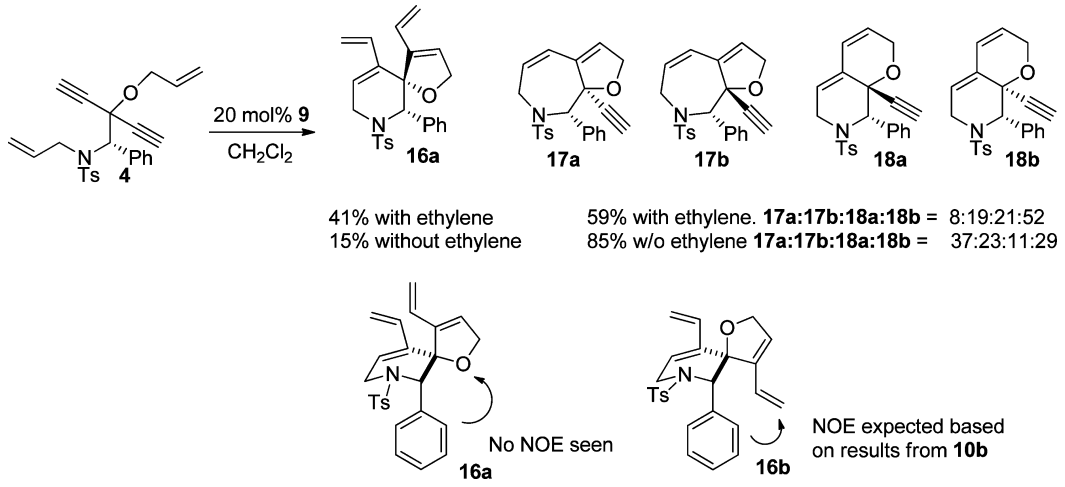
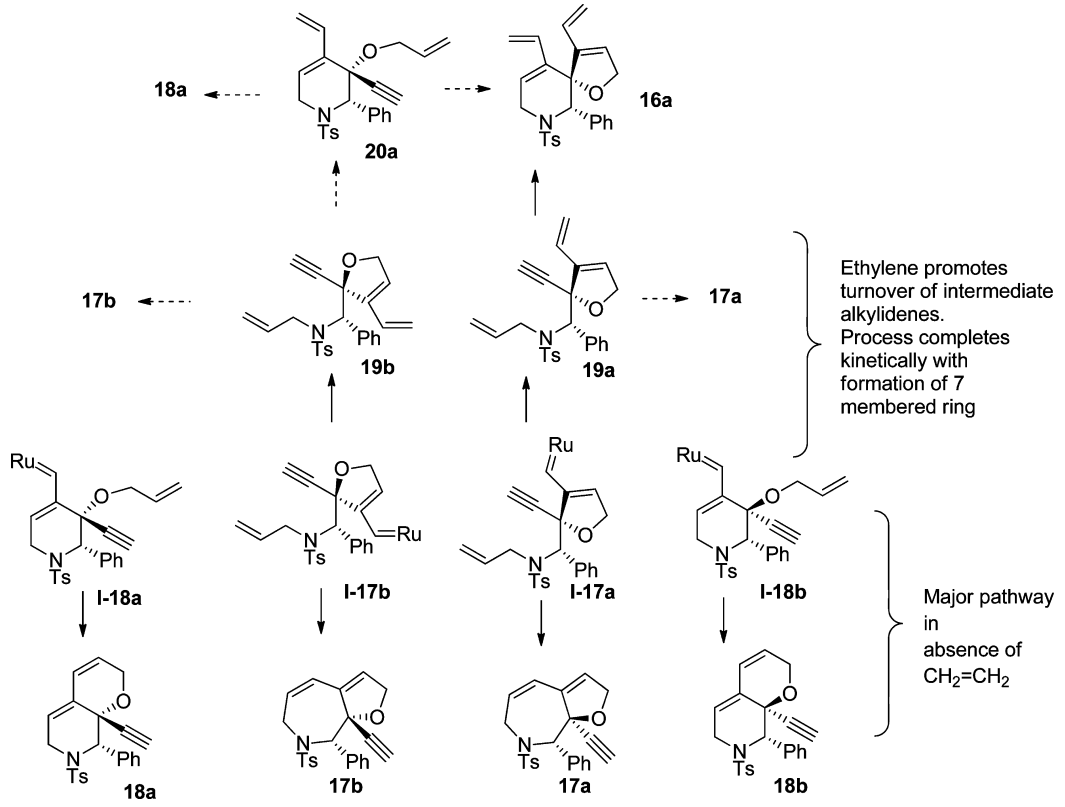
Scheme 6. Ring-Closing Metathesis of 4 Promoted by 9



Scheme 7. Proposed Intermediates in the Ring-Closing Metathesis Reaction of 4



different, with **17a** now formed as the major product, whereas this had been the minor component when ethylene was used (Scheme 6).

On the basis of the ratios of product seen in these reactions some insight into the reaction pathway and relative rates of the ring-forming steps can be gained. We propose the initial interaction of the catalyst would be with either of the unhindered alkene groups, followed by cyclization onto one of the two alkynes to generate intermediate vinyl carbenes **I-17a** and **b**, and **I-18 a** and **b** (Scheme 7).[23] In the absence of ethylene the primary reaction of these vinyl carbenes should be cyclization onto the remaining alkene to afford the observed **17a,b** and **18 a,b** in a combined HPLC yield of 85%.[11] When ethylene is present, turnover of the intermediate carbenes could be facilitated (by reaction with ethylene), and alternate reactions such as formation of spirocycle **16** could compete with direct formation of **17a,b** and **18a,b**. These alternate cyclizations would be expected to be particularly significant for reaction of **I-17a** and **I-17b** where subsequent formation of the 7-membered ring might be slower than competing processes. Experimentally, this appears to be the case as smaller amounts of both **17a** and **17b** are seen in the reaction with ethylene, with **17a** particularly reduced. On the basis of the stereochemistry of spirocycle **16a** we propose that **I-17a** is the major contributor to the formation of this compound in the presence of ethylene, at the expense of **17a**. Although no spirocycle is formed directly from **I-17b** (**16b** is not observed in any significant quantities in the reaction), other metathesis

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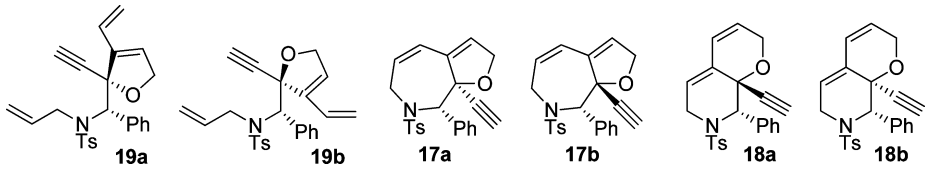
Table 2. Ring-Closing Metathesis Products of 4 Resulting from Reaction with 13



conditions	conversion (%)	19a	19b	17a	17b	18a	18b
20% 13 + CH_2CH_2	65	17	15	<1	25	31	12
40% 13 + CH_2CH_2	83	17	16	<1	25	31	11
20% 13	60	18	2	1	55	19	4
40% 13	94	11	1	1	58	17	5

processes may compete with 7-membered ring formation leading to reduced amounts of **17b** in reactions with ethylene present—for example ring-opening in **19b** could lead to inversion of the quaternary center and ultimately afford **16a** as well.

Finally, the reaction of **4** promoted by first-generation catalyst **13** was studied. These reactions were found to be slow; with 20 mol % catalyst about 60% conversion of starting material (with or without ethylene) was seen, and even with 40 mol % of **13** some **4** remained. No spirocyclic compounds (**16a** or **16b**) were formed; instead a mixture of the dienyne products **17** and **18** and some monocyclic intermediates (**19** and/or **20**) result (Table 2). As previously, in the absence of ethylene the concerted mechanism of dienyne ring-closing is the predominant pathway with a single monocyclic intermediate remaining. In the presence of ethylene, breakdown of the intermediate carbenes is accelerated, and about 30% of two inseparable monocyclic intermediates are isolated in addition to compounds **17a,b** and **18a,b**. Unambiguous structural identification of the monocyclic intermediates was challenging as they are inseparable from both each other and residual starting material; however, they are thought to be **19a** and **19b** on the basis of the following arguments. In the absence of ethylene compound **17b** becomes the major component of the mixture at the expense of one of the above-mentioned monocyclic intermediates, leading to its assignment as **19b** (both **19b** and **17b** would be formed from a common intermediate, **I-17b** in Scheme 7). The other monocyclic compound is thought to be **19a** as high selectivity for formation of **I-17b** over **I-17a** is not anticipated on the basis of studies with related substrates.[8d] The higher barrier to cyclization for the subsequent seven-membered ring adds further support that this intermediate is **19b** rather than isomers of **20** (see Scheme 7 for structure of **20**). Although neither isomer of **20** is seen, the formation of **18a** and **18b** suggests that **I-18a** and **I-18b** are intermediates, but are rapidly consumed, accounting for their nondetection.

CONCLUSION

In conclusion, we have evaluated ring-closing metathesis reactions of two bis(enynes). The expected spirocyclic products from a double ring-closing enyne cyclization can be formed in good yield when employing a reactive catalyst and where competing metathesis pathways are not possible, i.e. for cyclization of **3** promoted by **9**. However, in cases where a concerted dienyne pathway can compete, this process is generally favored, although running the reaction under ethylene partially inhibits dienyne metathesis. Under unique conditions we have also observed Diels–Alder and cyclopropanations products, and formation of these products were found to be stereoselective. Further studies on the competing mechanisms and reactions pathways for these reactions are underway in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION

General. Reactions were carried out under a nitrogen atmosphere, other than those which were specifically quoted as being run under an ethylene atmosphere. In these cases an ethylene filled balloon was used to both degas the solvent and then maintain the ethylene atmosphere. Reactions were monitored by reverse-phase HPLC, using an Ascentis Express C18 column (100 mm × 4.6 mm, 2.7 μm fused-core particle size) and eluting with mixture of 0.1% aq H_3PO_4 and MeCN. HPLC ratios and conversions are based on absolute integration and not corrected. Most reaction mixtures were purified using an automated purification system with prepacked silica gel columns. In some cases complete removal of residual solvent or minor reaction impurities was not possible; in these cases, quoted yields are adjusted as accurately as possible. ^{1}H and ^{13}C NMR spectra were recorded at either 400, 500, or 600 MHz, and unambiguous assignment of signals was made using a combination of NMR experiements, including COSY, 1D-TOCSY, HMBC, and HSQC. Where applicable 1D NOE experiments were used to assign relative stereochemistry, and these results are presented in the Supporting Information section. High-resolution mass spectra were recorded on a QTOF API US mass spectrometer by electrospray ionization.

*Bis(enyne) **3**.* To a stirred, cooled (−10 °C) solution of alcohol **5** (320 mg, 0.932 mmol) and propargyl bromide (693 mg, 4.66 mmol) in THF (5.0 mL) and DMPU (2.0 mL) was added sodium hydride (298 mg, 60 wt %, 7.45 mmol). The reaction was allowed to warm to room temperature over 2 h and stirred for a further 16 h at the same temperature. The reaction was quenched by cautious addition of water (10 mL) and 1.0 *M* HCl (10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated under vacuum, and then purified on an automated purification system using a 40 g prepacked silica column, eluting with 5% ethyl acetate in hexane increasing to 10% ethyl acetate in hexanes. The product **3** was collected as a colorless oil (277 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, d, J = 8.1 Hz) 7.57 (2H, m), 7.23 (3H, m), 7.17 (2H, d, J = 8.1 Hz), 6.13 (1H, dd, J = 17.5, 10.9 Hz), 5.73 (1H, dd, J = 17.6, 11.0 Hz), 5.43 (1H, dd, J = 17.6, 1.2 Hz), 5.39 (1H, dd, J = 10.9, 1.1 Hz), 5.27–5.22 (2H, m,), 5.01 (1H, s), 4.63 (1H, dd, J = 18.9, 2.4 Hz), 4.44 (1H, dd, J = 18.9, 2.4), 4.08 (1H, dd, J = 15.3, 2.4 Hz), 4.00 (1H, dd, J = 15.3, 2.4 Hz), 2.43 (1H, t, J = 2.4 Hz), 2.39 (3H, s), 1.92 (1H, t, J = 2.4 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 137.5, 136.1, 135.9, 135.6, 131.0, 129.0, 128.2, 127.9 (2C), 119.5, 119.0, 86.9, 80.7, 80.1, 73.6, 71.6, 67.0, 52.6, 35.4, 21.4. ; HRMS Calc for $C_{25}H_{25}NO_3S$+Ag 526.0606, found 526.0608.

*Alcohol **7**.* To a solution of methyl ester **6** (2.52 g, 7.89 mmol) in THF (20 mL) was added a solution of ethynylmagnesium bromide (63.1 mL, 0.5 *M* in THF, 31.5 mmol) at room temperature. After 1 h the mixture was heated to 50 °C and stirred for 2 h after which time HPLC analysis indicated complete conversion. The reaction was cooled to room temperature and quenched with NH_4Cl (30 mL, sat.

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aq) and 1.0 *M* HCl (10 mL) After stirring for a further 15 min the mixture was extracted with ethyl acetate (2 × 40 mL), the combined organics were washed with brine (40 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude solid was purified on an automated purification system using an 80 g prepacked silica column, eluting with 20% ethyl acetate increasing to 40% ethyl acetate. The alcohol **7** was isolated as a white solid, 1.98g, 65%.

Mp = 161−162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (2H, d, J = 8.1 Hz), 7.23−7.21 (3H, m), 7.17 (2H, m), 7.08 (2H, d, J = 8.1 Hz), 5.87 (1H, d, J = 9.1 Hz), 4.62 (1H, d, J = 9.1 Hz), 3.31 (1H, br, s), 2.64, (1H, s), 2.55 (1H, s), 2.33 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.83, 136.86, 134.67, 129.26, 128.63, 128.40, 127.83, 127.2, 80.45, 80.34, 75.49, 75.11, 66.38, 65.81, 21.42; HRMS; Calc for $C_{19}H_{17}NO_3S$+Ag 445.9980, found 445.9986.

Bis(enyne) ***4***. To a solution of alcohol **5** (540 mg, 1.59 mmol) in DMF (10 mL) at room temperature was added sodium hydroxide (382 mg, 9.55 mmol) followed by allyl bromide (0.48 mL, 5.57 mmol), and the mixture stirred for 4 h at the same temperature. The reaction was diluted with water (20 mL) and extracted with isopropyl acetate (2 × 20 mL). The combined organics were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude solid was purified on an automated purification system using a prepacked 80 g silica column eluting with 10% ethyl acetate in hexane, increasing to 20% ethyl acetate in hexane. The product **4** was isolated as a white solid, 382 mg, 57%.

MP = 114−115 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (2H, d, J = 8.1 Hz), 7.71 (2H, m), 7.31 (3H, m), 7.20 (2H, d, J = 8.1 Hz), 5.93−5.91 (1H, m), 5.75 (1H, s), 5.72−5.71 (1H, m), 5.32 (1H, dd, J = 15.9, 1.6 Hz), 5.19 (1H, dd, J = 9.2, 1.5 Hz), 5.00 (1H, dd, J = 17.3, 1.4 Hz), 4.89 (1H, dd, J = 10.3, 1.3 Hz), 4.36- 4.32 (2H, m), 4.13−4.11 (1H, m), 3.91 (1H, dd, J = 16.5, 7.5 Hz), 2.58 (1H, s), 2.57 (1H, s), 2.40 (3H, s).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 138.0, 136.3, 135.8, 133.8, 130.3, 128.9, 128.5, 128.1, 127.9, 117.1, 115.9, 80.0, 79.7, 76.9, 76.3, 72.6, 67.4, 67.1, 49.1, 21.5. HRMS Calc for $C_{25}H_{25}NO_3S$+Ag 526.0606, found 526.0602.

Ring Closing Metathesis of ***3*** *Promoted by* ***9***. A solution of bis(enyne) **3** (56 mg, 0.133 mmol) in dichloromethane (5 mL) was degassed by subsurface nitrogen purge. Zannan catalyst **9** (18 mg, 0.024 mmol) was added and the flask flushed with ethylene and maintained under an ethylene atmosphere for the duration of the reaction. After 2 h the reaction showed no further change based on HPLC analysis and was concentrated under vacuum. After concentration the relative ratio of the two compounds was unchanged. The two spirocyclic compounds were separated using an automated purification system on a 24 g prepacked silica column, eluting with 5% ethyl acetate in hexanes, increasing to 20% ethyl acetate in hexanes to afford **10a** (16 mg, 28%) and **10b** (25 mg, 45%).

Major product ***10b:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (2H, d, J = 8.1 Hz), 7.22−7.17 (5H, m), 7.17 (2H, d, J = 8.1 Hz), 6.41−6.32 (2H, m), 5.85 (1H, s), 5.27 (1H, s), 5.23−5.18 (4H, m), 5.10 (1H, d, J = 17.7 Hz), 4.83 (1H, dd, J = 12.1, 2.0 Hz), 4.78 (1H, dd, J = 12.1, 1.5 Hz), 4.18 (1H, dd, J = 17.2, 1.6 Hz), 3.70 (1H, dd, J = 17.2, 1.5 Hz), 2.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 141.1, 136.9, 136.8, 135.6$_1$, 135.6$_0$, 129.1 (3C), 128.5$_6$, 128.5$_4$, 128.0, 127.6, 127.5, 117.8, 115.0, 87.7, 72.6, 63.2, 40.2, 21.4; HRMS Calc for $C_{25}H_{25}NO_3S$ +Ag 526.0606, found 526.0599.

Minor product ***10a:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, d, J = 8.1 Hz), 7.22−7.17 (5H, m), 7.14 (2H, d, J = 8.1 Hz), 6.48 (1H, dd, J = 17.7, 10.8 Hz), 6.35 (1H, dd, J = 17.8, 11.0 Hz), 5.84 (1H, s), 5.75 (1H, s), 5.26−5.15 (3H, m), 5.24 (1H, s), 5.05 (1H, d, J = 17.7 Hz), 4.82−4.75 (2H, m), 4.34 (1H, dd, J = 16.6, 1.4 Hz), 3.57 (1H, dd, J = 16.6, 1.6 Hz), 2.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 138.3, 136.3, 136.2, 135.2, 135.1, 131.4, 130.5, 129.9, 129.3, 129.0, 128.0, 127.7, 127.3, 117.4, 114.0, 88.7, 74.2, 62.6, 40.9, 21.4; HRMS Calc for $C_{25}H_{25}NO_3S$+Ag 526.0606, found 526.0603.

Ring Closing Metathesis of ***3*** *promoted by* ***13***. A solution of bi(enyne) **3** (54 mg, 0.129 mmol) in dichloromethane (5 mL) was degassed by subsurface nitrogen purge. Grubbs catalyst **13** (21.0 mg, 0.025 mmol) was added and the flask flushed with ethylene and maintained under an ethylene atmosphere for the duration of the reaction. After 20 h there was no further change in the product ratio, and the mixture was concentrated under vacuum; the major products were isolated by use of an automated purification system with a 12 g prepacked silica column, eluting with 5% ethyl acetate in hexanes, increasing to 20% ethyl acetate in hexanes to afford a mixture of **14**, **15**, **10a**, and **10b** in a combined yield of 82%. The two new products were purified further on a ChiralPak AS 21 mm × 250 mm column eluting with 30% MeOH in CO_2.

Diels−Alder product ***14:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (2H, d, J = 8.1 Hz), 7.26−7.21 (5H, m), 7.19 (2H, d, J = 8.1 Hz), 6.06 (1H, dd, J = 17.0, 10.8 Hz), 5.64 (1H, m), 5.50 (1H, m), 5.20 (1H, dd, J = 17.0, 1.2 Hz), 5.09 (1H, dd, J = 10.8, 1.2 Hz), 4.52 (1H, d, J = 14.5 Hz), 4.44 (1H, m), 4.32 (1H, m), 4.20 (1H, s), 4.01 (1H, d, J = 14.5 Hz), 3.04 (1H, m), 2.50 (2H, m), 2.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 139.4, 138.9, 137.2, 136.4, 129.9, 129.7, 128.9, 128.0, 127.3, 126.9, 124.6, 116.9, 115.0, 85.0, 68.4, 64.5, 47.6, 47.5, 27.7, 21.5; HRMS; Calc for $C_{25}H_{25}NO_3S$+Ag 526.0602, found 526.0598.

Cyclopropane ***15:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, J = 8.1 Hz), 7.28−7.24 (5H, m), 7.16 (2H, d, J = 8.1 Hz), 6.44 (1H, dd, J = 17.8, 11.0 Hz), 5.83 (1H, br t, J = 1.4 Hz), 5.66 (1H, dd, J = 17.3, 10.7 Hz), 5.23 (1H, d, J = 17.8), 5.19 (1H, d, J = 11.0 Hz), 5.11 (1H, s), 5.02 (1H, dd, J = 10.7, 0.7 Hz), 4.98 (1H, dd, J = 17.3, 0.7 Hz), 4.20 (1H, dd, J = 17.3, 1.6 Hz), 4.12 (1H, d, J = 8.5 Hz), 3.88 (1H, d, J = 8.5 Hz), 3.72 (1H, dd, J = 17.3, 1.4 Hz), 2.36 (3H, s), 1.24 (1H, dd, J = 8.2, 4.6 Hz), 1.01 (1H, t, J = 4.6 Hz), 0.81 (1H, dd, J = 8.2, 4.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 136.8$_4$ (2C), 136.8$_0$, 136.6, 135.6, 129.2, 128.8, 128.7, 128.0, 127.4, 126.6, 114.8, 113.6, 81.2, 68.8, 60.2, 40.6, 33.0, 31.5, 21.4, 13.4. HRMS; Calc for $C_{26}H_{27}NO_3S$+Ag 540.0763, found 540.0766

Ring-Closing Metathesis of ***4*** *with* ***9***. A solution of bis(enyne) **4** (49 mg, 0.117 mmol) in dichloromethane (4 mL) was degassed by subsurface nitrogen purge. Zannan catalyst **9** (18 mg, 0.024 mmol) was added and the flask flushed with ethylene and maintained under an ethylene atmosphere for the duration of the reaction. After 2 h the reaction showed no further change based on HPLC analysis and was concentrated under vacuum. After concentration the ratio of products was unchanged. The spirocyclic compound **16a** was separated from the dienyne products using an automated purification system on a 24 g prepacked silica column, eluting with 5% ethyl acetate in hexanes, increasing to 20% ethyl acetate in hexanes to afford **16a** (14.7 mg, 30%) and a mixture of **17a,b** and **18a,b** (22.5 mg, 49%). The relative ratios of **17a,b** and **18a,b** were determined by ^{1}H NMR spectroscopy on the mixture, having obtained pure samples from preparative HPLC.

The "without ethylene" reaction was carried out in a similar manner, excluding the ethylene flush and the reaction was maintained under a nitrogen atmosphere. In this case 12% of **16a** was isolated and 65% of a mixture of **17a,b** and **18a,b**.

Spirocycle ***16a:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (2H, d, J = 8.1 Hz), 7.19−7.13 (5H, m), 7.00 (2H, d, J = 8.1 Hz), 6.28−6.21 (2H, m), 6.10 (1H, s), 6.07 (1H, m), 5.63 (1H, d, J = 17.6 Hz), 5.42 (1H, d, J = 17.6 Hz), 5.27 (1H, s), 5.25 (1H, d, J = 13.3), 5.10 (1H, d, J = 11.1 Hz), 4.61 (2H, AB q J = 14.6 Hz) 4.25 (1H, dd, J = 18.1, 4.3 Hz), 3.61 (1H, d, J = 18.1 Hz), 2.30 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ143.7, 142.9, 138.5, 137.6, 135.3, 133.0, 129.0, 128.9, 128.1, 128.0, 127.6, 127.5, 121.9, 119.5, 117.7, 115.6, 88.3, 74.1, 63.6, 42.2, 21.4; HRMS; Calc for $C_{25}H_{25}NO_3S$+Ag 526.0606, found 526.0600.

Separation of ***17a,b*** *and* ***18a,b***. A mixture of compounds **17a,b** and **18a,b** from a number of combined metathesis reactions were separated on a ChiralPak AD 30 mm × 250 mm column eluting with 25% MeOH in CO_2 to afford purified samples of each isomer.

17a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (2H, d, J = 8.1 Hz), 7.44 (2H, m), 7.32- 7.28 (3H, m), 7.15 (2H, d, J = 8.1 Hz), 6.09 (1H, d, J = 10.8 Hz), 5.91 (1H, dt, J = 10.8, 4.8 Hz), 5.63 (1H,br, s), 5.35 (1H, s), 4.83 (2H, s), 4.56 (2H, d, J = 4.8 Hz), 2.44 (1H, s), 2.40 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 139.7, 137.8, 137.4, 130.6, 128.8, 127.9, 127.7, 127.5, 127.4, 127.3, 123.5, 89.9, 81.7, 77.0, 74.6, 67.0, 43.6, 21.5; HRMS; Calc for $C_{23}H_{21}NO_3S$+Ag 498.0293, found 498.0294.

17b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (2H, d, J = 8.1 Hz), 7.35 (2H, m), 7.24−7.22 (5H, m), 6.35 (1H, d, J = 11.8 Hz), 5.86 (1H, dt, J

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= 11.8, 5.5 Hz), 5.71 (1H, br, s), 5.66 (1H, s), 4.65 (1H, d, J = 14.4 Hz), 4.46 (1H, dd, J = 17.7, 4.0 Hz), 4.14−4.09 (2H, m), 2.40 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 138.2, 136.5, 135.9, 129.3, 129.2, 128.0, 127.8, 127.7, 127.6$_8$, 126.5, 123.2, 86.0, 83.8, 74.6, 74.3, 66.5, 44.9, 21.4; HRMS; Calc for $C_{23}H_{21}NO_3S$+Ag 498.0293, found 498.0300.

18a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (2H, d, J = 8.1 Hz), 7.28−7.20 (5H, m), 7.12 (2H, d, J = 8.1 Hz), 6.22 (1H, d, J = 10.1 Hz), 5.90 (1H, dd, J = 10.1, 3.2 Hz), 5.63 (1H, s,), 5.61 (1H, br t, J = 3.2 Hz), 4.59 (1H, d, J = 16.8 Hz), 4.26 (1H, d, J = 18.7 Hz), 4.13 (1H, dd, J = 16.8, 3.7 Hz), 3.72 (1H, d, J = 18.7 Hz), 2.48 (1H, s), 2.36 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 136.2, 135.8, 131.2, 129.4, 129.1, 128.0 (2C), 127.9, 127.7, 122.7, 118.6, 82.3, 73.8, 69.6, 62.4, 62.3, 42.3, 21.4; HRMS; Calc for $C_{23}H_{21}NO_3S$+Ag 498.0293, found 498.0310.

18b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (2H, d, J = 8.1 Hz), 7.52 (2H, m), 7.32 (3H, m), 7.23 (2H, d, J = 8.1 Hz), 6.01 (1H, d, J = 9.9 Hz), 5.89 (1H, dd, J = 9.9, 3.9 Hz), 5.59 (1H, m), 4.79 (1H, s), 4.41 (2H, m), 4.23 (1H, d, J = 17.5 Hz), 4.16 (1H, dd, J = 17.2, 4.3 Hz), 2.42 (3H, s), 2.37 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 138.6, 136.0, 135.8, 129.4, 128.9, 127.7$_5$, 127.7$_0$, 127.5, 127.3, 122.3, 120.8, 79.0, 76.9, 72.2, 66.3, 61.7, 43.0, 21.5; HRMS; Calc for $C_{23}H_{21}NO_3S$+Ag 498.0293, found 498.0288.

Reactions of **4** with first-generation catalyst **13** were carried out using procedures comparable to those listed above. In these cases an inseparable mixture of starting material **4** and monocyclic compounds were isolated in addition to compounds **17a,b** and **18a,b**.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, discussion of NOE studies and copies of NOE spectra for **10b**, **10a**, **14**, **15** along with discussion of stereochemical assignment for **17a,b** and **18a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Trace amounts (about 2%) of cyclopropane **15** were also detected in reactions with **9**. The Diels–Alder product **14** was not observed.
(21) On the basis of unidentified minor components in the mixture the selectivity for formation of **16a** over **16b** is thought to be >95:5.
(22) Although assignment of stereochemistry based on the absence of NOE interactions is nonoptimum, in this case we are confident of the interpretation, as the data can be compared to those obtained for spirocycles **10a** and **10b** where both isomers were available for study.
(23) To simplify structures ligands on ruthenium are not shown in the intermediate vinyl carbenes.