Pergamon

Tetrahedron Letters 40 (1999) 3247–3250

TETRAHEDRON
LETTERS

Spirocycle Assembly Through Selective Tandem Ring Closing Metathesis Reactions

Martin J. Bassindale[a], Peter Hamley[b], Andreas Leitner[a] and Joseph P.A. Harrity*[a]

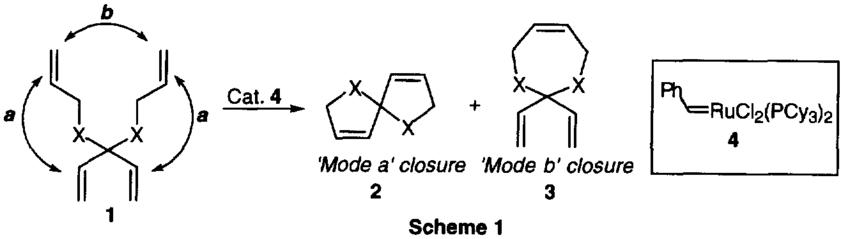
[a]*Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, S3 7HF*

[b]*Department of Medicinal Chemistry, Astra Charnwood, Bakewell Road, Loughborough, LE11 5RH*

Received 12 January 1999; accepted 17 February 1999

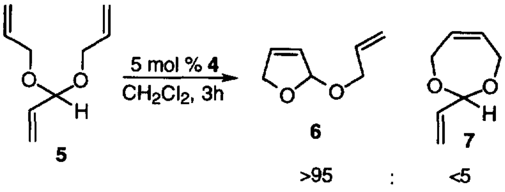
Abstract: A range of functionalised spirocyclic systems have been prepared under mild and neutral conditions by tandem selective ring closing olefin metathesis reactions. Additionally, a marked preference for 5-membered ring closure over 7-membered ring closure was observed which appears to be a result of a kinetically favoured cyclisation process. © 1999 Elsevier Science Ltd. All rights reserved.

Transition metal catalysed ring closing olefin metathesis has recently emerged as one of the most powerful techniques available for the construction of carbo- and heterocyclic compounds.[1] In this context, we wished to exploit this technique in a novel spirocycle assembly through the employment of two tandem ring closing metathesis reactions on a tetraalkene. As outlined in Scheme 1, tetraene **1** can undergo ring closing metathesis through two modes leading to two different products. Desired spirocyclisation would require selective metathesis through *mode a* to provide **2**, whereas monocyclic product **3** would result from cyclisation through *mode b*.[2]



Scheme 1

We were confident that 5-membered ring formation would be the dominant process, however as 7-membered ring closure is known to be readily accomplished under mild conditions,[3] it was unclear as to the level of selectivity of spirocyclisation over the competing process. In an effort to gauge the likely selectivity of *mode a* cyclisation over *mode b*, we prepared a simple model substrate **5**[4] and examined its behaviour on treatment with catalytic quantities of Grubbs's Ru-catalyst **4**. As outlined in Scheme 2, we were pleased to find that 5-membered ring cyclisation proceeded with complete selectivity to afford dihydrofuran **6** with no detectable quantity of cyclic acetal **7** (250MHz ^{1}H NMR).[5]

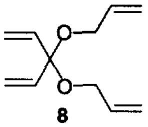
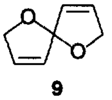
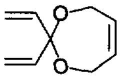
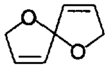
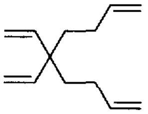
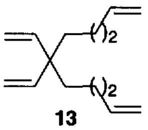
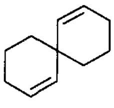
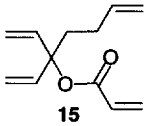
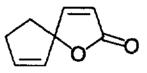


Scheme 2

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00375-5

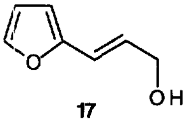
We next turned our attention to developing this selective metathesis process into a novel, catalytic, and general technique for the assembly of functionalised spirocyclic systems. We therefore examined the reaction scope using a range of tetraolefinic precursors, the results are outlined in Table 1.[6]

Table 1: Ru-catalysed spirocyclisation[a]

Entry	Substrate[b]	Product	Yield
1	 **8**	 **9**	90%
2	 **10**	 **9**	50%[c]
3	 **11**	 **12**	98%
4	 **13**	 **14**	92%
5	 **15**	 **16**	62%[d]

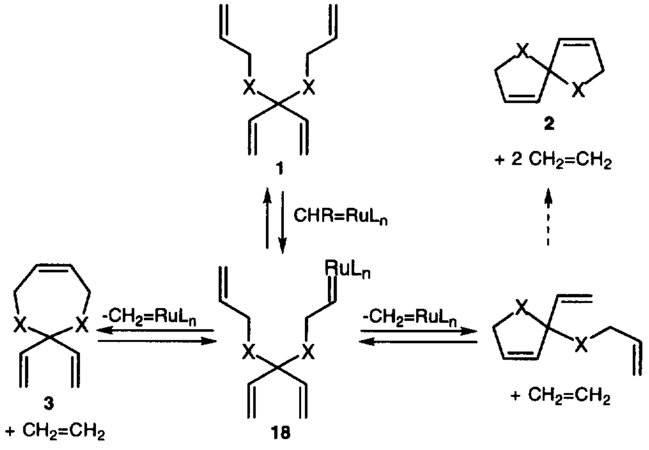
[a]All reactions carried out in 0.1M CH_2Cl_2 at 25°C with 5 mol % of **4** and were complete within 6h unless otherwise indicated.
[b]All substrates prepared under routine conditions, see reference 6.
[c]Carried out at 40°C with 15 mol % of **4** over 36 hours.
[d]Carried out at 40°C with 8 mol % of **4** over 48 hours.

Our initial studies focused on the preparation of spirocyclic acetal **9**. As outlined in Entry 1, the high selectivity for 5-membered ring formation was observed in the spirocyclisation process such that **9** was readily assembled from **8** under mild conditions. Notably, spiroacetal **9** rapidly decomposes to furan **17** on treatment with catalytic TsOH at room temperature within 1 hour. This result suggests that functionalised [4,4]-spiroacetals such as **9** cannot be accessed by traditional acid catalysed techniques,[7,8] however, they are prepared in excellent yield under these newly developed neutral metal catalysed spirocyclisation conditions. Additionally and notably, seven-membered ring cyclic compounds can also provide the desired spirocycles as exemplified in Entry 2. Cyclic acetal **10** provides **9**, albeit in moderate yield, after addition of 15 mol % catalyst in refluxing CH_2Cl_2 over 48 hours.


17

Subsequently, this technique was extended and readily applied to the preparation of spirocyclic carbocycles such as **12** (Entry 3) and to the homologous six membered ring isomer **14** (Entry 4). Both reactions proceeded quickly and efficiently at room temperature. Additionally, butenolide **16** could also be accessed. In contrast, this reaction was found to be sluggish, affording the product in moderate yield after heating in refluxing dichloromethane with portionwise addition of catalyst over 48 hours.[9]

A plausible mechanism for the selective spirocyclisation process is outlined in Scheme 3. It is likely that initiation takes place at the less hindered alkene to provide alkylidene **18**.[10] At this stage it is possible that selective cyclisation originates from a kinetically favoured 5-membered closure. Alternatively, 7-membered ring formation may effectively compete with 5-membered ring closure. However, if this process is reversible the reaction may be driven forward to the spirocyclic product on entropic grounds (*i.e.* by releasing an extra equivalent of ethylene). On the other hand, the observation that cyclic acetal **10** was unreactive when exposed to the catalyst at room temperature for over 12 hours and was only partially converted to **9** with higher catalyst loadings at elevated temperatures over a 36 hour reaction period strongly suggests that formation of **3** is only very slowly reversible and that the observed selectivity for spirocyclisation is the result of a kinetic preference for 5-membered ring closure rather than an entropically driven process.



Scheme 3

In conclusion, we have demonstrated that a selective tandem ring closing metathesis process provides an efficient technique for the preparation of a variety of functionalised spirocyclic systems under mild conditions. In the case of [5,5]-spirocycles, the cyclisation reaction appears to be kinetically driven although we have found that 7-membered ring formation is reversible under more forcing conditions.

Acknowledgments: We gratefully acknowledge support from Astra Charnwood (MJB) and the University of Sheffield.

References and Notes

1. For recent reviews on the ring closing metathesis reaction in organic synthesis see: (a) Armstrong, S.K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (b) Grubbs, R.H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.

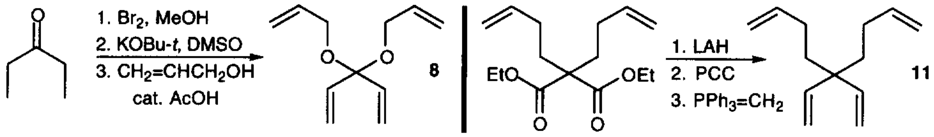
2. Metathesis of the penta-1,4-diene unit to a cyclopropene was not considered. For related references see: (a) Huwe, C.M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376. (b) Michaut, M.; Parrain, J.-L.; Santelli, M. *Chem. Commun.* **1998**, 2567.

3. (a) For example see: Barrett, A.G.M.; Baugh, S.P.D.; Gibson, V.C.; Giles, M.R.; Marshall, E.L.; Procopiou, P.A. *Chem. Commun.* **1996**, 2231. (b) For an example of cyclohexene formation over cyclopentene cyclisation see: Kirkland, T.A.; Grubbs, R.H. *J. Org. Chem.* **1997**, *62*, 7310. (c) For an example of cyclohexene formation over spirocyclic cyclopentene formation see: Dyatkin, A.B. *Tetrahedron Lett.* **1997**, 38, 2065.

4. Mutterer, F.; Morgen, J.M.; Bieldermann, J.M.; Fleury, J.P.; Weiss, F. *Bull. Chim. Soc. Fr.* **1979**, 4478.

5. The reaction mixture was analysed by ^{1}H NMR in comparison to an authentic sample of **7**.

6. All substrates and products exhibited satisfactory spectral and analytical data. Synthetic routes to **8** and **11** outlined below are representative:



Representative experimental procedure (compound **16**): A solution of ester **15** (60 mg, 0.312 mmol) in CH_2Cl_2 (3.1 ml) was treated with 2 mol % catalyst **4** (5 mg) and the mixture heated at reflux for 12 h. A further 6 mol % catalyst was added in 2 mol % portions at 12 h intervals and the reaction was found to be complete by TLC after a total of 48 h. The solvent was removed on rotary evaporation and the residue purified chromatographically on silica gel. Elution with 1:1 pentane:ether provided **16** as a pale yellow oil (26 mg, 62%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.20-2.25 (2H, m), 2.44-2.58 (1H, m), 2.64-2.78 (1H, m), 5.47 (1H, dt, *J*=5.5, 2.1 Hz), 6.04 (1H, d, *J*=5.5Hz), 6.23 (1H, dt, *J*=5.5, 2.4 Hz), 7.28 (1H, d, *J*=5.5Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 31.96, 33.05, 99.45, 120.40, 128.51, 139.76, 157.00, 172.63. FTIR (film) 1758 cm^{-1}. HRMS Calcd for $C_8H_8O_2$: 136.0524. Found: 136.0525.

7. Perron, F.; Albizati, K.F. *Chem. Rev.* **1989**, *89*, 1617.

8. For an approach to spirocycles using single ring closing metathesis see: (a) van Hooft, P.A.V.; Leeuwenburgh, M.A.; Overkleeft, H.S.; van der Marel, G.A.; van Boeckel, C.A.A.; van Boom, J.H. *Tetrahedron Lett.* **1998**, *39*, 6061. (b) Maier, M.E.; Bugl, M. *Synlett* **1998**, 1390.

9. Grubbs and co-workers have also observed that dienes containing electron withdrawing olefinic substituents are poor substrates in the ring closing metathesis reaction, see reference 3(b). For a related example see Rutjes, F.P.J.T.; Shoemaker, H.E. *Tetrahedron Lett.* **1997**, 38, 677. The referee pointed out that the slow reaction of **15** may also be due to the unfavourable conformational change in going from ester (*s*-cis) to lactone (*s*-trans).

10. Catalyst insertion into alkenes adjacent to a quarternary centre does not take place readily at room temperature: Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1996**, *118*, 100.