Enyne metathesis for the facile synthesis of highly functionalised novel bicyclic β-lactams

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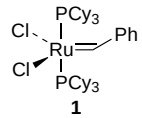
A wide range of bicyclic β-lactam systems have been prepared *via* the enyne metathesis reaction using catalytic quantities of *trans*-$(Cy_3P)_2Cl_2Ru{=}CHPh$ (Cy = cyclohexyl).

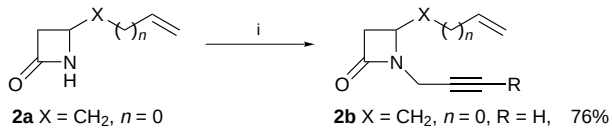
The elaboration of carbon skeletons *via* the construction of carbon–carbon bonds represents one of the most important endeavours in synthetic organic chemistry. The use of catalytic quantities of ruthenium[1] and molybdenum[2] carbenes as pioneered by Grubbs *et al.* for ring-closing metathesis (RCM)[3] is exemplary in this respect and is finding increasing use as the key synthetic step *en route* to polyfunctional natural products.[4] As a variant on RCM of dienes, Kinoshita and Mori have demonstrated the catalytic ability of ruthenium carbene **1** to generate conjugated dienes (with concomitant rearrangement of the carbon skeleton) from enynes.[5] Recently we have reported the use of ring-closing and cross metathesis for the preparation of novel monocyclic and bicyclic β-lactams in a synthetically fast and efficient manner.[6,7] The possibility of utilising enyne metathesis as a route into highly functionalised bicyclic β-lactams appeared attractive and herein we disclose our results in this arena.



1

Cy = cyclohexyl

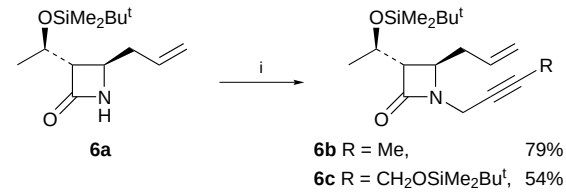
A broad range of enyne substrates were synthesised by two general routes. The previously prepared 4-substituted lactams **2a**–**5a**[6–8] were treated with prop-2-ynyl bromides in the presence of potassium hydroxide and tetrabutylammonium bromide to give variously functionalised enyne substrates **2b**–**5b**, **2c** (Scheme 1).§ Chiral, non-racemic enynes **6b** and **6c** were produced in an analogous fashion (Scheme 2). The *N*-allylated azetidinones **9** and **10** were synthesised using a modified procedure of Basak and Khamrai[9] for the introduction of the prop-2-ynyl group followed by *N*-allylation in the usual manner (Scheme 3).



2a X = CH_2, *n* = 0
3a X = CH_2, *n* = 1
4a X = O, *n* = 1
5a X = NTs, *n* = 1

2b X = CH_2, *n* = 0, R = H, 76%
2c X = CH_2, *n* = 0, R = Me, 58%
3b X = CH_2, *n* = 1, R = Me, 83%
4b X = O, *n* = 1, R = Me, 60%
5b X = NTs, *n* = 1, R = Me, 51%

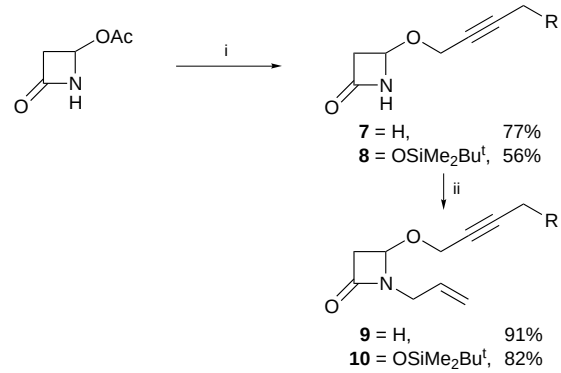
Scheme 1 *Reagents and conditions*: i, $BrCH_2C{\equiv}CR$, KOH, $Bu_4N^+Br^-$, THF, 0 °C, 2 h



6a

6b R = Me, 79%
6c R = $CH_2OSiMe_2Bu^t$, 54%

Scheme 2 *Reagents and conditions*: i, $BrCH_2C{\equiv}CR$, KOH, $Bu_4N^+Br^-$, THF, 0 °C, 2 h



7 = H, 77%
8 = $OSiMe_2Bu^t$, 56%

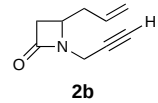
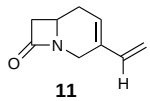
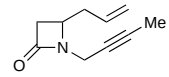
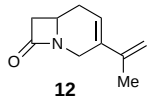
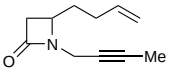
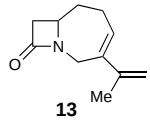
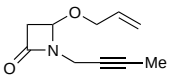
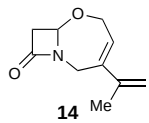
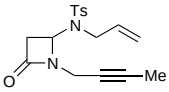
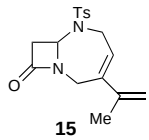
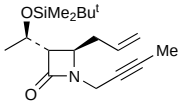
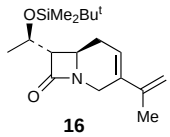
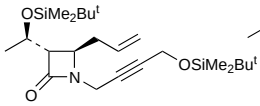
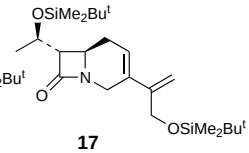
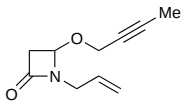
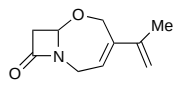
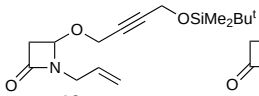
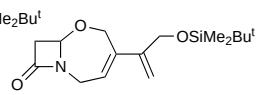
9 = H, 91%
10 = $OSiMe_2Bu^t$, 82%

Scheme 3 *Reagents and conditions*: i, $HOCH_2C{\equiv}CH_2R$, $Zn(OAc)_2$, PhMe, 120 °C; ii, $BrCH_2CH{=}CH_2$, NaH, DMF, 0 °C, 2 h

Attempts to bring about the cyclisation of the parent enyne **2b** were unsuccessful even with catalyst loadings of up to 10 mol% **1**: only starting material was recovered (Table 1, entry 1). However, the non-terminal enyne **2c** was found to undergo metathesis with as little as 1 mol% carbene **1**, albeit in 20% yield. Increasing amounts of catalyst gave increasing quantities of products and at 10 mol% catalyst **1** an 88% yield of **12** was obtained (Table 1, entry 2).¶ Under similar conditions enyne substrates **3b**–**6b**, **6c**, **9** and **10** furnished dienes **13**–**19** in similarly excellent yields (Table 1, entries 3–9). The range of

functionalities and steric bulk tolerated by this reaction, combined with the high yields obtainable for these cyclisations, make this a valuable addition to the procedures currently available for synthesising such complex β-lactam structures. Further applications of alkene and enyne metathesis will be reported in due course.

Table 1 Enyne metathesis using ruthenium carbene **1**[a]

Entry	Enyne	Product	**1** (Mol%)	Yield[b] (%)
1	 **2b**	 **11**	1	0
			10	0
2	 **2c**	 **12**	1	20
			5	52
			10	88
3	 **3b**	 **13**	10	82
4	 **4b**	 **14**	10	88
5	 **5b**	 **15**	10	70
6	 **6b**	 **16**	10	100
7	 **6c**	 **17**	15	72
8	 **9**	 **18**	5	48
			10	74
9	 **10**	 **19**	10	82

[a] All reactions carried out on *ca*. 0.25 mmol scale as a 0.1 M solution in CH_2Cl_2 with catalyst for 3 h. [b] Isolated yield after column chromatography.

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Footnotes

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§ All new compounds were fully characterised by spectroscopic data, microanalysis and/or HRMS.
¶ Typical experimental procedure: to enyne **2c** (50 mg, 0.30 mmol) was added a solution of catalyst **1** (21 mg, 0.03 mmol) in CH_2Cl_2 (3 ml). The solution was heated to reflux for 3 h, concentrated and chromatographed on silica (4 : 1 diethyl ether–hexane) to produce carbacephem **12** (44 mg, 88%) as a colourless oil.

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