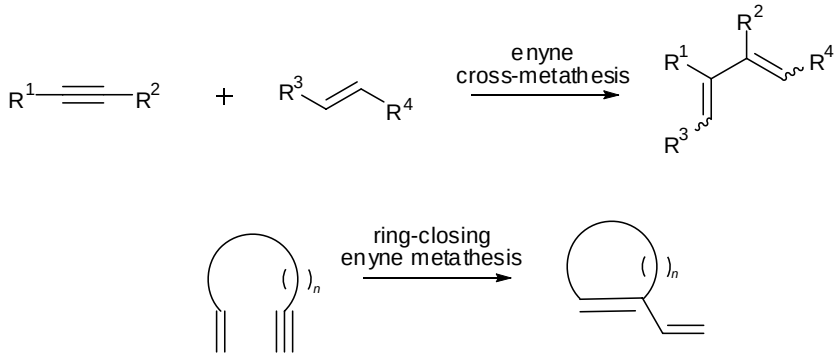
Lisa Fishlock 17th October 2006

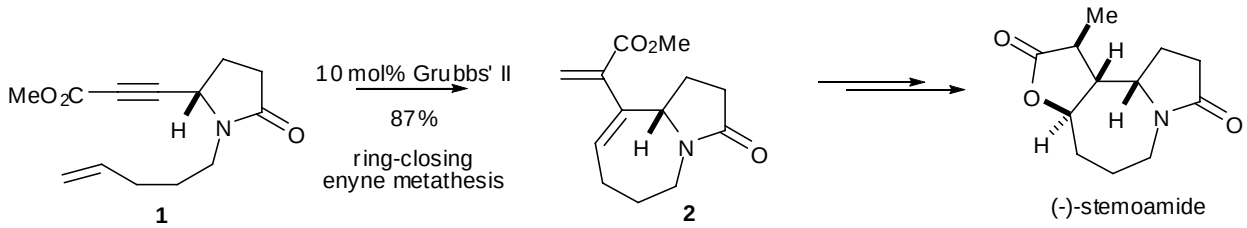
The Enyne-Metathesis Reaction

The enyne metathesis is a bond reorganisation of an alkene and an alkyne to produce a 1,3-diene (**Scheme 1**). It has been used in both intramolecular and intermolecular applications, and is driven by the enthalpic stability of the 1,3-diene produced. Stereoselection is often low in intermolecular cases but can be controlled in intramolecular cases.



Scheme 1

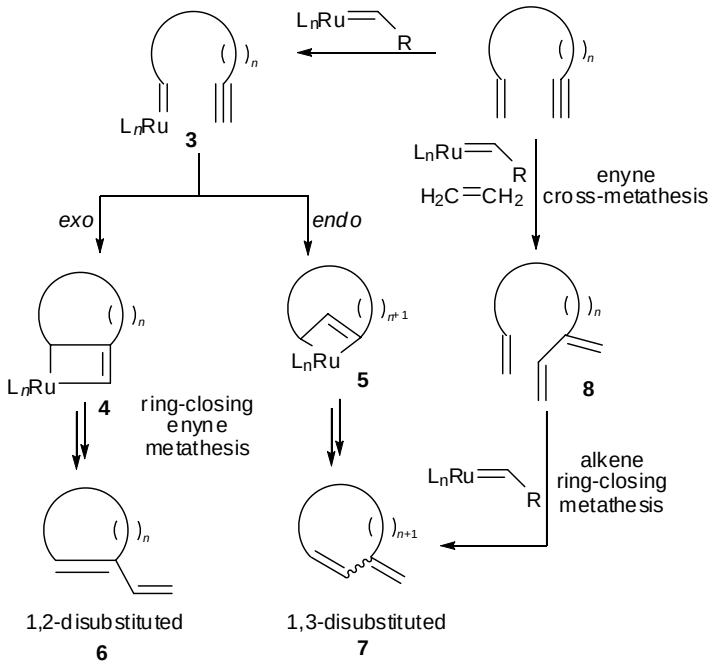
Mori and co-workers first pioneered the use of ruthenium carbene complexes in enyne-metathesis chemistry in 1994. Shortly afterwards, in 1996, the group published the synthesis of (–)-stemoamide; this was the first application of the enyne-metathesis reaction in a total synthesis (**Scheme 2**). The key step was the enyne ring-closing metathesis of precursor **1** using Grubbs' second generation catalyst, which furnished the bicyclic product **2** in 87% yield and without any erosion of stereochemical integrity at the sensitive propargylic position. With this advanced intermediate in hand, only a few more steps were required to arrive at the targeted product.



Scheme 2

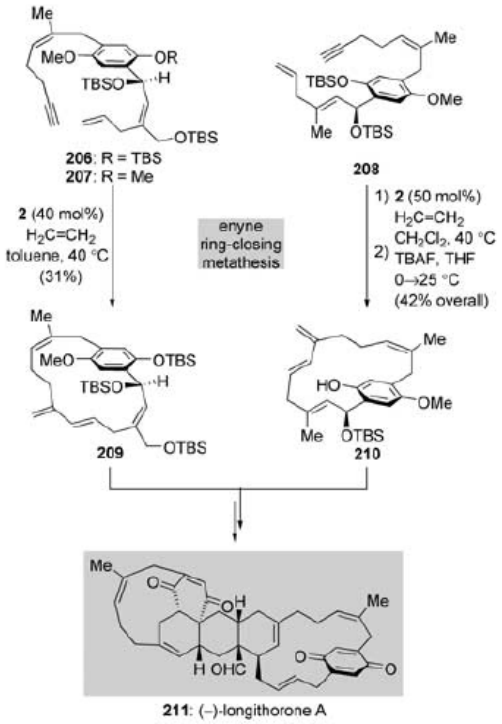
The intramolecular enyne-metathesis reaction also offers a useful method for the synthesis of macrocyclic ring systems (**Scheme 3**). However, when applying the enyne ring-closing metathesis reaction to the synthesis of large rings, a number of selectivity issues arise relating to the orientation of ring closure. The ruthenium carbene intermediate **3** can undergo two possible modes of ring closure, termed *endo* and *exo*. These two pathways generate different metallacyclobutene intermediates **4** and **5**, which subsequently yield the 1,2-disubstituted product **6** and 1,3-disubstitued product **7** respectively. The formation of common and medium sized rings by enyne ring-closing metathesis is typically constrained to follow an *exo* path, whereas macrocyclisations generally follow the *endo* mode of ring closure owing to the increased flexibility of the tether.

Enyne metathesis macrocyclisations are generally conducted under an atmosphere of ethylene; therefore, the metathesis reaction is believed to be directed away from the direct intramolecular enyne metathesis reaction which is inherently slow due to the effective concentration of the reacting termini. Instead, a two-step process has been proposed involving intermolecular enyne cross-metathesis with ethylene to generate **8**, which subsequently undergoes a conventional intramolecular alkene ring-closing metathesis reaction. The less sterically hindered terminal double bond of the butadiene moiety would be expected to be engaged selectively in the macrocyclisation to give the formal *endo* enyne metathesis product.



Scheme 3

In 2002, Shair and co-workers published the synthesis of the marine natural product (–)-longithorone A, which was inspired by the biogenetic hypothesis of the Schmitz group. The route employed a sequence of inter- and intramolecular Diels-Alder reactions to form much of the polycyclic architecture of the natural product (**Scheme 4**). This led them to conceive the macrocyclic compounds **209** and **210** as key synthetic intermediates. Recognising the characteristic 1,3-disubstituted butadiene system embedded within both compounds, the group planned to construct both intermediates through enyne ring-closing metathesis reactions. The cyclisation of both precursors with Grubbs' first generation catalyst under an ethylene atmosphere proved successful with both excellent atropselectivity and *E*/*Z* selectivity. In the absence of an ethylene atmosphere macrocyclisation did not occur, therefore it is likely that both cyclisations proceed through the two-step process.



Scheme 4

For reviews, see: *Angew. Chem. Int. Ed.*, **2005**, *44*, 4490-4527; *Chem. Rev.*, **2004**, *104*, 1317-1382. For synthesis of (–)-Stemoamide, see: *J. Org. Chem.*, **1996**, *61*, 8356-8357. For synthesis of (–)-Longithorone A, see: *J. Am. Chem. Soc.*, **2002**, *124*, 773-775.