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Digest Paper

Application of catalytic *Z*-selective olefin metathesis in natural product synthesis

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ABSTRACT

Over the last few years, a number of olefin metathesis catalysts have been disclosed that enable the synthesis of energetically disfavoured *Z*-alkenes. The application of this method to the synthesis of complex natural products has driven the development of new catalysts and furthered the understanding of their behaviour and reactivity. This digest discusses the progress made and highlights the benefits of this chemistry over more traditional protocols.

Contents

Introduction

Olefin metathesis (OM) has evolved into one of the most powerful reactions available to synthetic chemists for constructing carbon-carbon double bonds.[1] Since its discovery, OM has found widespread application in organic chemistry including natural product synthesis,[1b,2] the construction of heterocycles and arenes,[3] chemical biology[4] and industrial polymerisation processes.[5]

One of the features of traditional OM is the predictable stereoselectivity of the reaction. Cross-metathesis (CM) is typically *E*-selective, with the largest substituents *trans* disposed across the double bond, owing to the lower energy of *E*-alkenes and the reversible nature of the OM reaction pathway. The formation of higher energy *Z*-alkenes has generally been limited to ring-closing metathesis (RCM) in small ring sizes where ring strain inhibits the formation of *E*-alkenes. Formation of *Z*-alkenes in CM has relied upon the use of silicon tethers, to mask the CM as an RCM, which can be removed at a later stage[6] and a small number of cases where substrate control in determining the stereochemical outcome is possible.[7]

In recent years, however, a new range of OM catalysts has been developed to overcome these problems and enable general, catalyst controlled, formation of *Z*-alkenes from simple,

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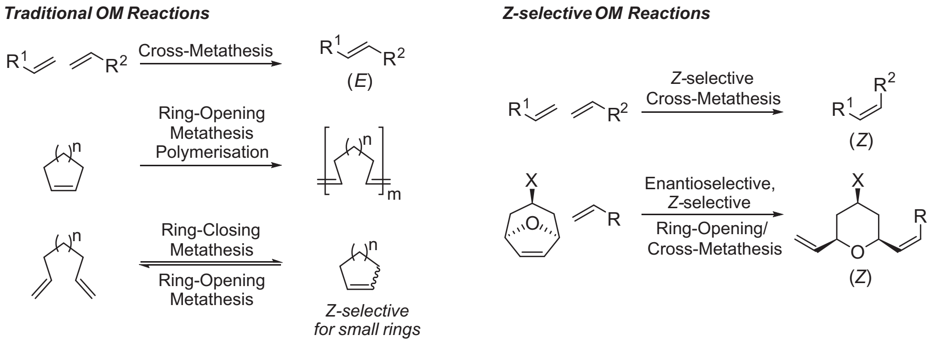


Scheme 1. Overview of traditional and *Z*-selective OM reactions.

unfunctionalised, starting materials. Alongside their application to traditional OM reactions, an enantioselective, desymmetrising, ring-opening/cross-metathesis (ROCM) protocol has been reported using these catalysts (Scheme 1).[8]

Z-Selective metathesis catalysts

A catalyst capable of kinetic *Z*-selective OM must overcome the thermodynamically favoured formation of *E*-alkenes. The reversible reaction pathway of OM means that it must also inhibit secondary metathesis, whereby a *Z*-alkene can be isomerised to the more stable *E*-alkene, to prevent erosion of *Z*/*E* selectivity.

One of the first *Z*-selective OM catalysts, developed by Schrock and Hoveyda, was the stereogenic-at-Mo monoaryloxide-pyrrolide (MAP) system **1** (Fig. 1). Similar Mo- and W-based systems, including the stereogenic-at-W MAP catalyst **2**, have subsequently been discovered to provide a collection of catalysts with a range of stabilities and activities.[8,9] In general, W complexes are less reactive than the Mo catalysts and are thus more suitable for less hindered olefins where the more active Mo species would display increased propensity for secondary metathesis and alkene isomerisation. Grubbs and Hoveyda have also independently developed complementary stereogenic-at-Ru based systems **3** and **4**. These are bench stable and either commercially available or easily accessible from known catalyst complexes (Fig. 1).[8,10]

All catalyst systems developed so far rely on steric differentiation between axially disposed ligands to induce kinetic stereoselectivity. In general, alkene substituents are orientated away from the bulky mesitylene ligand in the Ru-based systems and the freely rotating aryloxide ligand in the Mo/W catalysts. In both cases the formation of *E*-alkenes is inhibited by the steric proximity of one alkene substituent to the bulky axial ligand in the transition state (Scheme 2).[8,11]

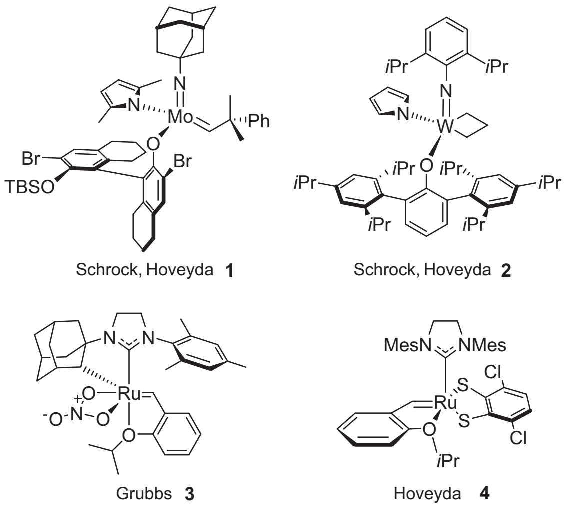
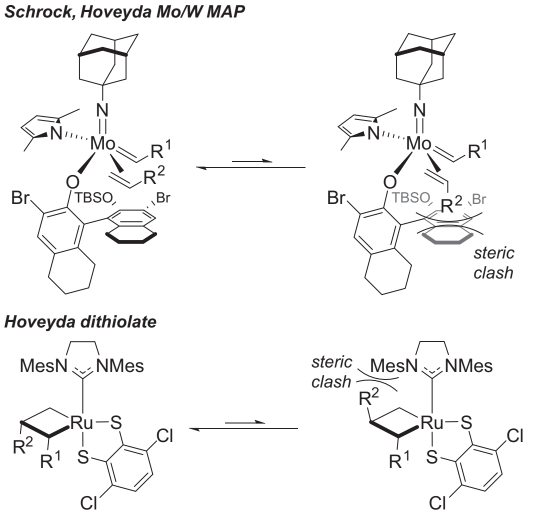

Schrock, Hoveyda **1**
Schrock, Hoveyda **2**
Grubbs **3**
Hoveyda **4**

Figure 1. Structures of some *Z*-selective metathesis catalysts.



Scheme 2. Proposed origin of *Z*-selectivity for catalysts **1** and **4**.

Typical reactivity in *Z*-selective OM

A range of *Z*-selective OM reactivity is exhibited by all of the catalysts above including enantioselective ROCM of bicyclic ring systems[11a] (Scheme 3, a), homodimerisation of terminal alkenes[12] (b) and CM of terminal and internal alkenes[10b] (c).

All of these reactions proceed to give the intended products in high yields and with high stereoselectivity. Moreover, the reactions show impressive functional group tolerance, highlighting the orthogonal reactivity exhibited by OM.

Z-Alkenes in natural products

Z-Alkenes are present in many biologically important natural products and over the last few years the novel *Z*-selective OM procedures highlighted have been applied to the total synthesis of some of these molecules.[13] A series of challenges were overcome in the course of these investigations. Sterically unhindered olefins, susceptible to secondary metathesis, could be prepared in high selectivity and instances of functional group incompatibility could be circumvented using the broad substrate scope of OM. In