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Temperature-dependent isomerisation versus net fragmentation of secondary allylic alcohols with Grubbs' catalyst

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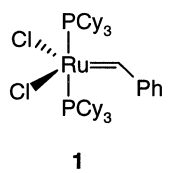
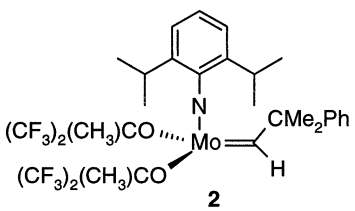
Abstract—Secondary allylic alcohols with 10 mol% of Grubbs catalyst in refluxing toluene/1,2-dichloroethane undergo isomerisation to ethyl ketones whereas with 100 mol% of Grubbs catalyst at room temperature, a net fragmentation reaction with the loss of a carbon atom occurs, to provide a methyl ketone. Probable mechanisms are described.

Ring-closing metathesis (RCM) is widely being used in organic synthesis for the construction of medium to large ring structures.[1] Among the two most widely used catalysts, namely Grubbs' ruthenium alkylidene catalyst **1**[2] and Schrock's molybdenum alkylidene catalyst **2**,[3] **1** is undoubtedly more exploited because of its inherent characteristic properties, particularly functional group compatibility, tolerance to many solvent systems, air and moisture insensitivity, and thermal stability even in refluxing toluene.[4]



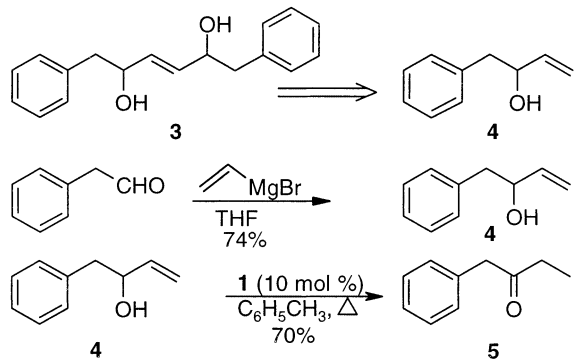
1



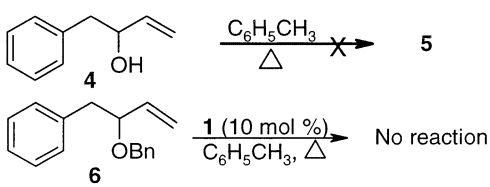
2

Cross-coupling metathesis, an emerging area of research whereby two symmetrical or non-symmetrical olefins combine to form open-chain olefinic compounds, has received relatively less attention.[5] As a part of our interest in HIV protease inhibitors,[6] we sought to develop a simple approach to construct 1,6-diphenyl-2,5-dihydroxy-hex-3-ene (**3**) by cross-coupling metathesis of 4-phenyl-1-buten-3-ol (**4**) using **1**. Compound **4** was prepared by vinyl magnesium bromide addition to phenyl acetaldehyde. Treatment of **4** with 10 mol% of **1** in refluxing toluene gave a product that did not conform with the expected product **3**. However, based on ^{1}H NMR, ^{13}C NMR, IR spectroscopy and elemental analysis, structure **5** was proposed for the new product. It was apparent that compound **5** was formed as a result of intramolecular hydrogen-transfer isomerisation of **4** (Scheme 1). Similar isomerisation was also noticed at lower temperature with dichloroethane under reflux. Isomerisation of allylic alcohols to ketones using catalytic amounts of ruthenium complexes has been reported previously.[7]

In the absence of catalyst **1**, compound **4**, in refluxing toluene, did not furnish compound **5**. The presence of a



Scheme 1.



Scheme 2.

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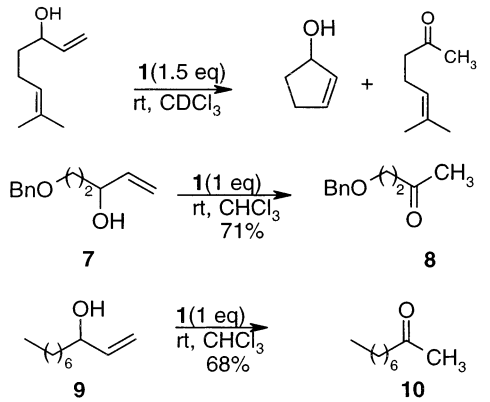

Scheme 3.

free alcohol group was essential[8] for the isomerisation because, under the above conditions, the *O*-benzyl derivative **6** was found to be inert (Scheme 2).

Our results were contrary to the observations recently reported by Hoye and Zhao[9] who noticed that a secondary allylic alcohol undergoes a net fragmentation reaction with 100 mol% of **1** at room temperature, leading to a methyl ketone, with the loss of one carbon atom (Scheme 3).

We also carried out the fragmentation reaction on substrates **7** and **9** with 100 mol% of **1** at room temperature and, indeed, observed the formation of methyl ketones **8** and **10** with the loss of a carbon atom. Based on the above observation, we proposed two hypothetical mechanistic pathways to explain the net fragmentation reaction (path A) and hydrogen-transfer isomerisation reaction (path B), since the conventional mechanism involving η^2 complexation of an alkene, followed by hydrogen transfer to the metal to form an η^3 intermediate,[10] is tedious for the present transformation (Scheme 4).

It seems that at higher temperature the process of hydrogen transfer precedes the *cyclo*-reversion reaction of metallocyclobutane leading to isomerisation. Final β-elimination from metallo intermediates **I** and **II** proceeds via C–C cleavage, followed by hydride transfer from ruthenium species, led to ethyl ketone as the product and regeneration of catalyst **1** (path B). Path B was supported by the detection of the enone-derivative as a minor component. For example, the 500 MHz ^{1}H NMR spectrum of the reaction product shown in entries 1, 2, 5 and 8 revealed, apart from major signals of ethyl ketone derivative, the characteristic resonances due to an enone functionality (CH_2=CH–C=O) between 5.77 and 5.88 ppm (double-doublet) and at 6.2 ppm (multiplet) distinctly different from the values observed for the precursor. Path A essentially endorses the mechanism proposed by Hoye and Zhao[9] to explain the loss of one carbon atom and the decomposition of catalyst **1** leading to a methyl ketone derivative.

Table 1 indicates that a large number of allylic alcohols can be isomerised in the presence of a catalytic amount of **1**[11] to provide the isomerised products (ethyl ketones)[13] and many protecting groups survived the transformation. The lack of reaction for entries 9 and 10 was attributed to steric factors.

In summary, this communication, for the first time, deals with studies on net fragmentation with stoichiometric amounts of Grubbs' catalyst and isomerisation with the more usual catalytic amounts of Grubbs' catalyst of secondary allylic alcohols and has examined their temperature dependence.

Acknowledgements

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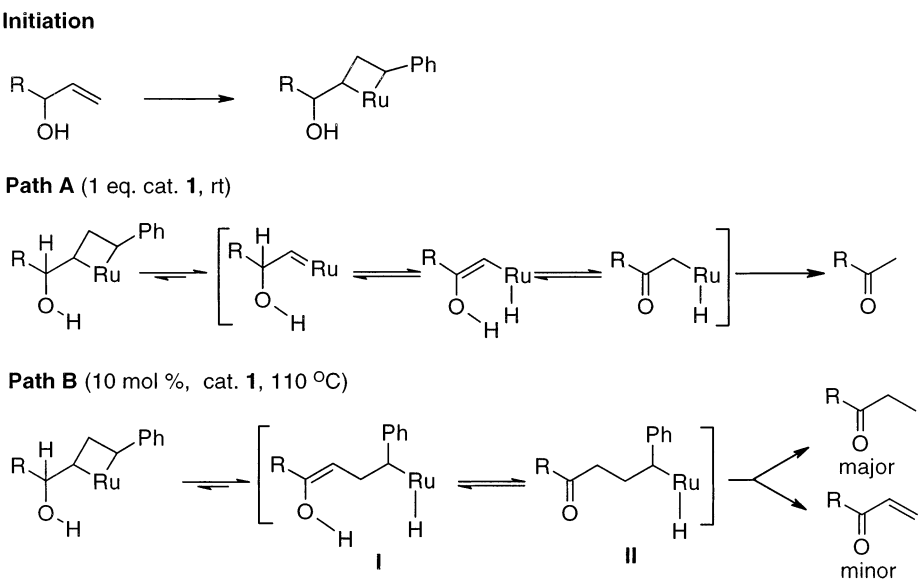
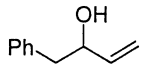
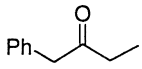
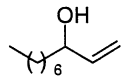
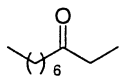
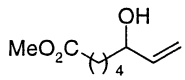
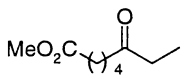
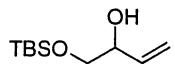
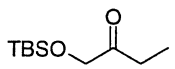
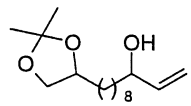
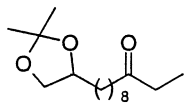
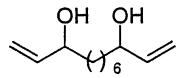
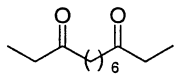
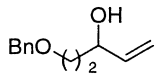
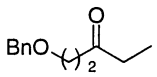
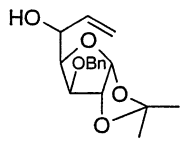
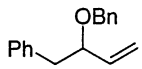


Scheme 4.

Table 1.

Entry	Allylic alcohol	Time (h)	Solvent[a]	Product	Yield (%)
1		2	A/B		70[12a]
2		2	A		80[12a]
3		3	A/B		67[12b]
4		4	A/B		67[12c]
5		2	B		70
6		1	B		81[12d]
7		1	B		52[12e]
8		24	B	–	–
9		24	B	–	–

[a] A is 1,2-dichloroethane; B is toluene.

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11. Grubbs' catalyst was purchased from Strem Chemicals Ltd, USA.
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13. General procedure for isomerisation: To the allyl alcohol (0.5 mmol) in refluxing 1,2-dichloroethane or toluene (2 ml), Grubbs' catalyst **1** (0.05 mmol) was added portionwise under an argon atmosphere. After completion of reaction (TLC), the solvent was evaporated and the residue was purified on silica gel using light petroleum and ethyl acetate as eluent.