



Ring-closing metathesis versus cross metathesis of resin-bound olefins

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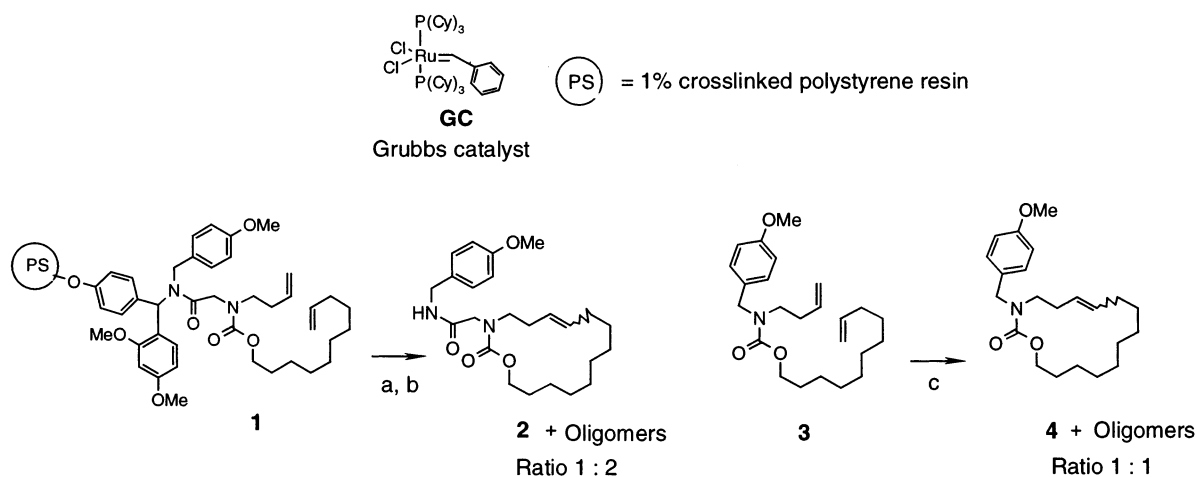
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Abstract—Resin-bound di-olefins were treated to metathesis conditions and both intramolecular ‘ring-closing’ metathesis (RCM) and intermolecular ‘cross’ metathesis were observed. Mono-olefin analogs produced dimers in high yield via intermolecular metathesis, despite being polymer-bound. The majority of resin-bound olefin molecules are able to come within reacting distance and 1% crosslinked polystyrene offers little or no ‘site separation’. This demonstrates a method to use olefin metathesis with the potential to prepare compound libraries on resin by dimerizing simple olefins into more complex molecules. © 2001 Elsevier Science Ltd. All rights reserved.

In the course of a study¹ of macrocyclic ring synthesis by ring-closing metathesis² (RCM) on resin-bound di-olefins, we reacted di-olefin **1** with the Grubbs catalyst³ **GC** to obtain, after cleavage from the resin,⁴ a minor amount of the 16-membered ring product **2** and a major amount of a mixture of products with molecular weight consistent with linear and cyclized dimers, trimers, etc. of di-olefin **1**. The ratio of **2** to oligomers was 1:2. Shown in Scheme 1, the same reaction performed in solution on related di-olefin **3** produced the related cyclic carbamate product **4** in a slightly improved 1:1 ratio relative to oligomers.

It was surprising to us that the resin-bound version of this di-olefin system produced increased intermolecular ‘cross’ metathesis, (Fig. 1, illustrated by B and C), versus intramolecular ‘ring-closing’ metathesis, (illustrated by A), relative to the solution phase reaction.⁵ Such intermolecular ‘cross’ metathesis was not observed previously when a resin-bound peptide di-olefin system^{6a} was reacted with **GC**, but has been observed with two, simple resin-bound mono-olefins.^{6b}

We synthesized a 17-membered ring precursor **5** and found that solution phase RCM produced only the



Scheme 1. (a) 30% **GC**, CH₂Cl₂, 45°C, overnight. (b) TFA cleavage. (c) 10% **GC**, CH₂Cl₂, 45°C, 2 h.

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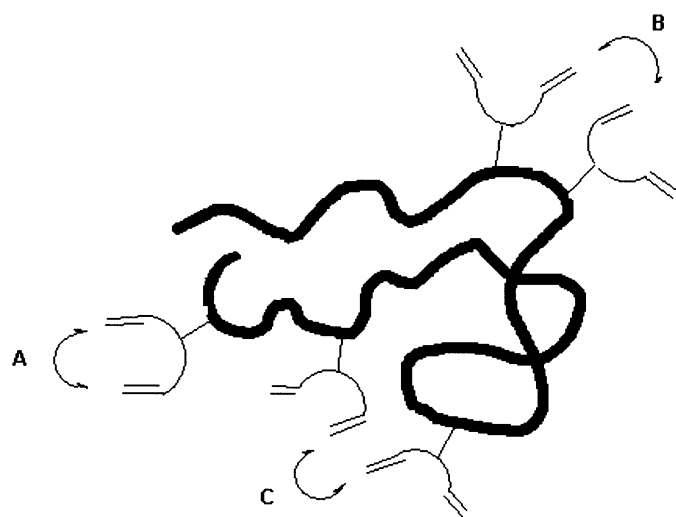


Figure 1. A shows intramolecular 'RCM', B and C show intermolecular 'cross metathesis', bold line represents polymer.

cyclized product **6** with no detectable dimers or oligomers. When this di-olefin system was synthesized attached to resin as analogous compound **7**, metathesis gave a mixture of cyclized product **8** and oligomers in a ratio of 1:2 (Scheme 2). These results comparing resin-bound systems to solution reactions show that resin bound di-olefins are not necessarily inhibited from intermolecular reaction, and under some conditions react intermolecularly even when the corresponding solution reaction proceeds by intramolecular reaction. It is clear a significant percentage of the resin bound olefin molecules can come within reacting distance of each other while still attached to the resin.

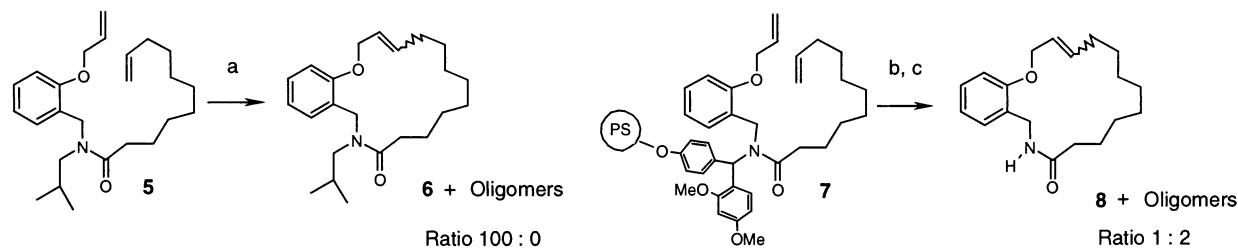
To study this further, we prepared the two resin-bound mono-olefin analogs **9** and **10** and reacted them with GC (Scheme 3). Unlike compounds **1**, **3**, **5** and **7**, ring-closing is no longer possible with these substrates

and we should be able to measure the extent these resin-bound olefins can come within reacting distance. Both materials were treated with 30 mol% GC at 45°C in methylene chloride for 16 h with the concentration of GC at 2 mM and the resin loading 0.55 mmol/g. Following cleavage and purification, **9** gave an 84% isolated yield of **11** and 8% recovered starting material, while **10** gave a 70% yield of **12** with 20% unreacted starting olefin. In each case, the only products observed were the metathesis 'dimers' **11** and **12**.

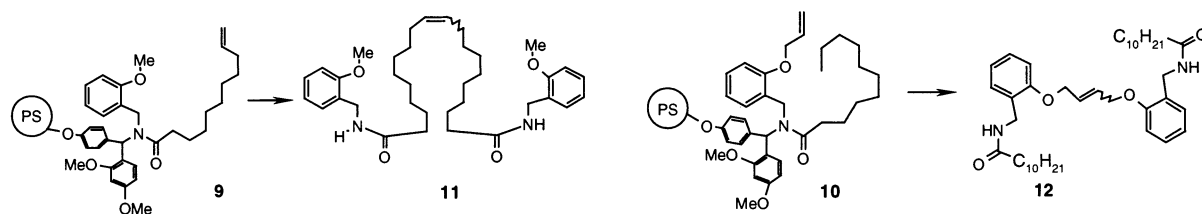
We could show the alkyl olefin compound **9** reacted faster than the allyl ether olefin **10** by a direct competition experiment where equal portions of resin-bound **9** and **10** were mixed and treated to the reaction conditions for 2 h. The resulting products were a mixture of 75% **11** and 25% **12**, indicating that the alkyl olefin converts to product faster than the allyl ether. This could reflect intrinsic reactivity differences between the olefins or indicate that the longer chain length in **9** allows the alkyl olefins greater opportunity to get within reacting distance than with the shorter chain length in **10**.

These results show that a minimum of 84% of the bound molecules on 1% crosslinked polystyrene are able to come within reacting distance while attached to the resin. 'Site-separation' of molecules attached to a flexible resin has been proposed and debated⁷ and supported by spectroscopic measurements.⁸ The metathesis results presented here add to the evidence that any site separation that may exist in a resin is not a physical separation and one should not assume attaching a molecule to a resin isolates it from being within reacting distance of another molecule anywhere along the polymer chain. These results were obtained using the common 1% crosslinked polystyrene resin and more rigid resins may not follow this pattern.

The ability to dimerize resin-bound olefins in good yield via metathesis demonstrates a method to create sym-



Scheme 2. (a) 10% GC, CH₂Cl₂, 45°C, 2 h. (b) 30% GC, CH₂Cl₂, 45°C, 2 h. (c) TFA cleavage.



Scheme 3.

metrical compounds on resin which are then linked to the resin via two attachment points. This provides the basis for preparing interesting libraries of compounds where a significant increase in molecular complexity is available by a single reaction step. Previously, solution-phase metathesis was used to prepare a library as a statistically controlled mixture of homo- and heterodimers.⁹ The resin-bound approach allows a controlled synthesis of pure homodimers which can be further modified by subsequent reactions on the resin-bound products.

References

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4. The Rink linker was used to attach the olefins to the resin, so cleavage was accomplished by shaking the resin with 10% TFA/methylene chloride at rt for 30 min.
5. Since all substrates are connected to the resin, we recognize that all reactions here could be considered ring-closing reactions, with the polymer backbone considered part of the ring. Thus, the term ring-closing metathesis is used herein to describe the case where the olefins react as pictured in A in Fig. 1 and cross metathesis to describe the olefin reaction partners as in B or C.
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