

Summary of Anna Michrowska Ph.D. research

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Recent years have seen a burgeoning of interest in olefin metathesis (Figure 1).^{1,2} Using this tool, chemists can now efficiently synthesize an impressive range of molecules that only a decade ago required significantly longer and tedious routes.³

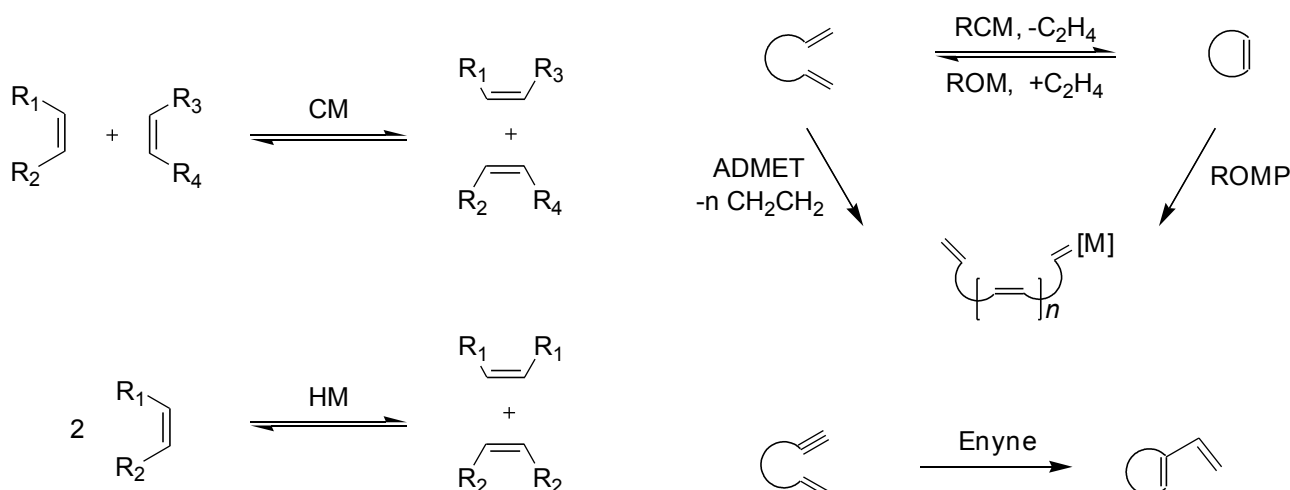


Figure 1: Olefin metathesis: RCM = ring-closing metathesis, ROM = ring-opening metathesis, ADMET = acyclic diene metathesis polymerization, ROMP = ring-opening metathesis polymerization, CM = cross-metathesis, HM = homo-metathesis

Especially, the development of efficient and selective ruthenium catalysts **2-4** has been the key to the widespread application of olefin metathesis in organic synthesis (Figure 2).⁴ Importance of metathesis was also noticed by the Royal Swedish Academy of Sciences. In the year 2005 the Nobel Prize in Chemistry was given to: Yves Chauvin, Robert H. Grubbs and Richard R. Schrock for their landmark work in this field.²

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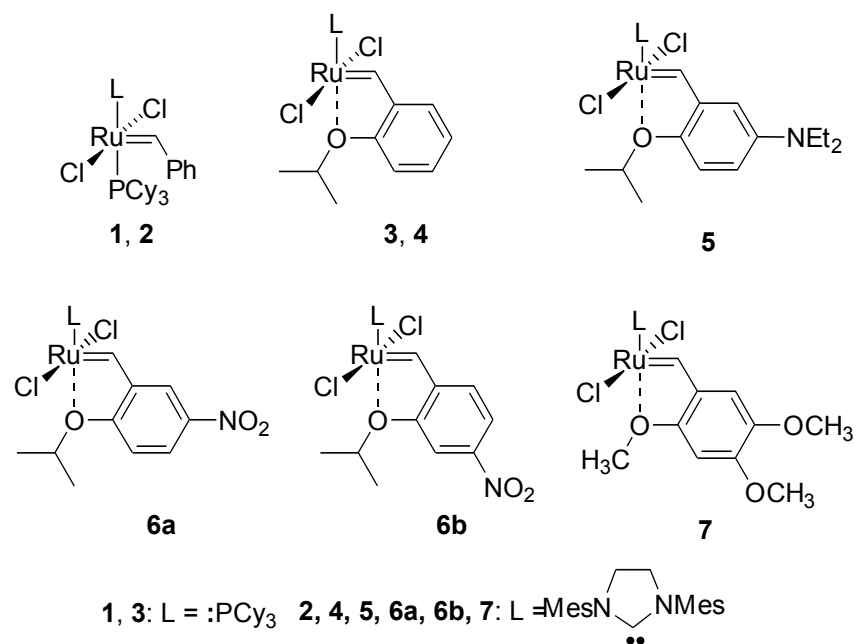


Figure 2: Ruthenium-based catalysts 1-5 for olefin metathesis (Cy = cyclohexyl, Mes = 2,4,5-trimethylphenyl).

During my PhD research I focused on developing new, more active and stable, Hoveyda-Grubbs type of catalysts, their applications in the olefin metathesis and extending the scope of this transformation.

First part of my work was devoted to the synthesis of Hoveyda-Grubbs type of catalysts modified in the benzylidene fragment. I have proposed a novel mode of activation of this ruthenium complexes, not by steric but by electronic effects. I have found that changing the electron density at the Ru-chelating oxygen of Hoveyda type complexes has direct impact on the both catalyst activity and stability. Especially, the stable 4- and 5-nitro-substituted Hoveyda catalysts (**6a**, **6b**), introduced in my work, exhibit impressive activity in ring-closing (RCM), cross (CM) and enyne-metathesis.⁵ Both of these complexes can operate under very mild conditions and are easy to prepare from commercially available substrates. As a result, these highly active⁶ catalysts have already found many successful applications in target-oriented syntheses⁷ and in the pharmaceutical industry⁸ (Figure 3).⁹

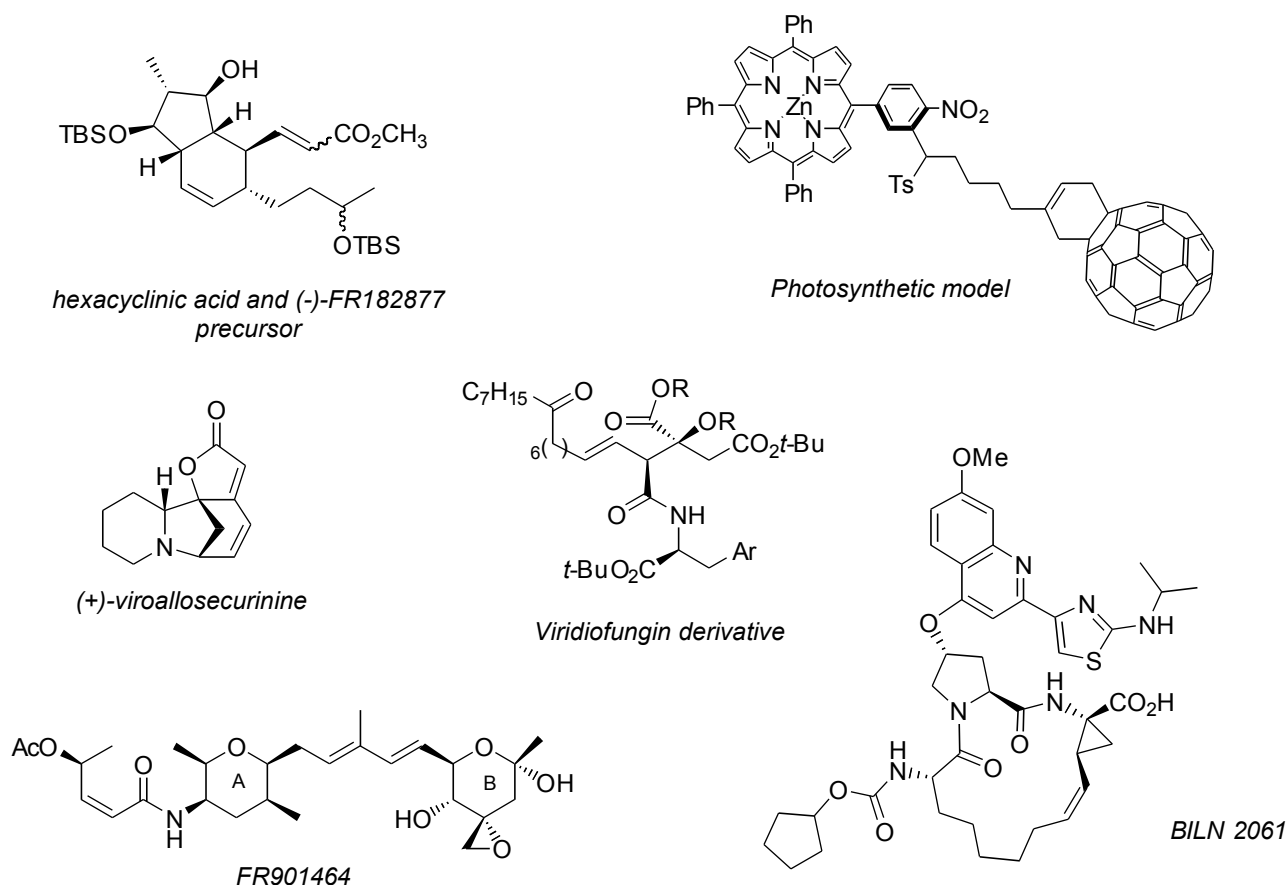


Figure 3: Selected applications of catalysts **6a** and **6b** in target oriented syntheses and in the pharmaceutical industry.⁹

I have also prepared a catalyst bearing an electron-donating (EDG) diethylamino group (**5**). After reaction with polymer-supported acids, the new ruthenium “amine” complex was conveniently immobilized by ion exchange (Figure 4a). In this was a novel strategy in which amino group plays a twofold role, being first an active anchor for immobilization and secondly, after protonation, activating the catalysts (*electron donating to electron withdrawing activity switch*). Furthermore, using the above described strategy of non-covalent immobilization I prepared catalyst **5P** immobilized on glass polymer composite Raschig rings (Figure 4b,c) which can be used for combinatorial chemistry and high-throughput screening.¹⁰ I have also demonstrated for the first time that RCM can be conducted under *PASSflow* continuous flow conditions using a non-covalently immobilized Ru-catalyst.¹¹

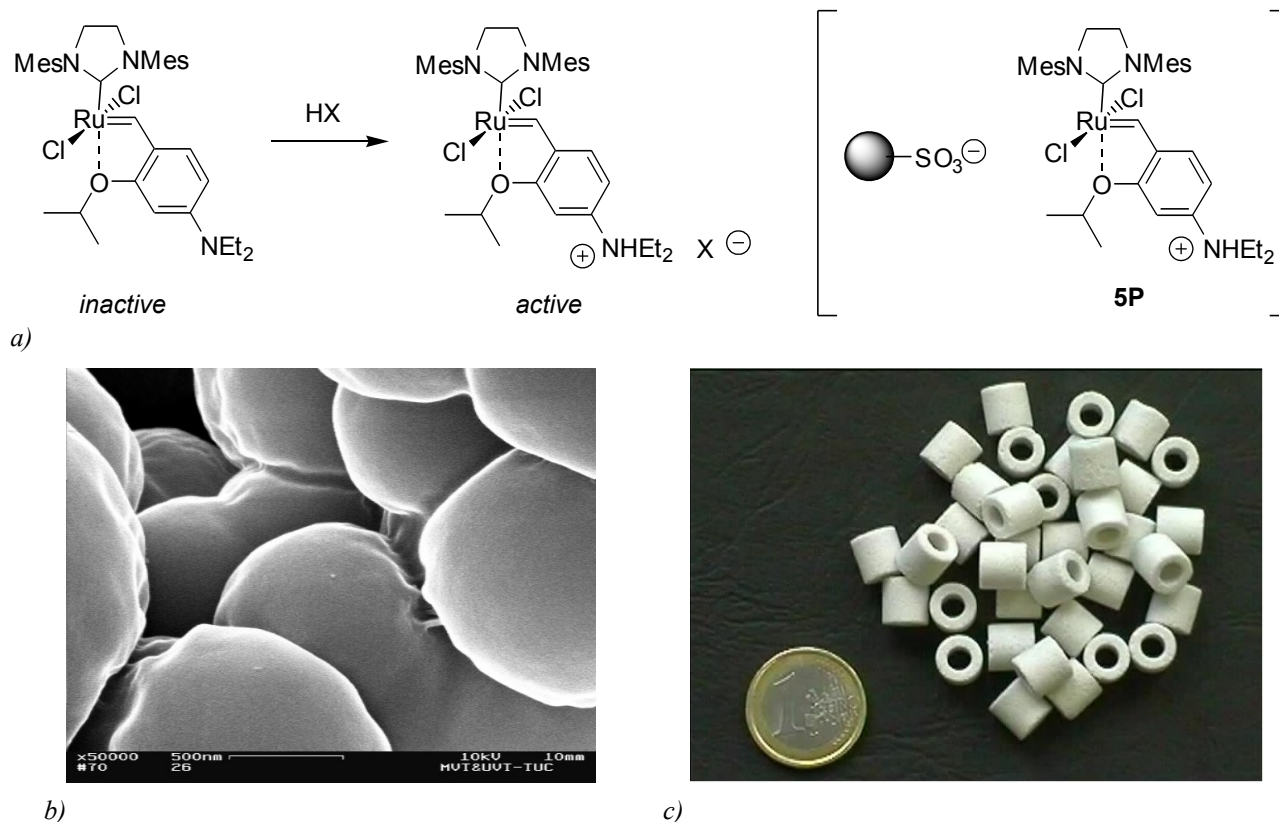


Figure 4: a) A principle of catalyst **5** activation and non-covalent binding of a catalyst to polymeric phase. b) Sulfonated polymer particles inside Raschig rings, as visualised by SEM. c) Megaporous glass Raschig rings used for immobilisation of catalyst **5**.

Moreover, I have proposed that substitution with functional groups can be used not only to fine-tune the catalyst activity but at the same time to introduce new physical properties, such as affinity to silica gel,¹² enhanced solubility in chosen media¹³ etc.

Exploring further the concept of catalyst activation *via* electron donation to electron withdrawing activity switch I have obtained complex **8** bearing a quaternary ammonium group (Figure 5).^{13,14} This catalyst exhibits higher activity than parent Hoveyda complex **4** and has, in comparison a high affinity for silica, enabling its efficient removal, in a single chromatographic pass (affording products of RCM in which the residual Ru content is typically below 100 ppm).^{13,15} In addition, the high efficiency of quaternary catalyst **8** in aqueous media, in conjunction with its facile removal from organic products, can be expected to offer new opportunities in green applications of olefin metathesis.¹⁶

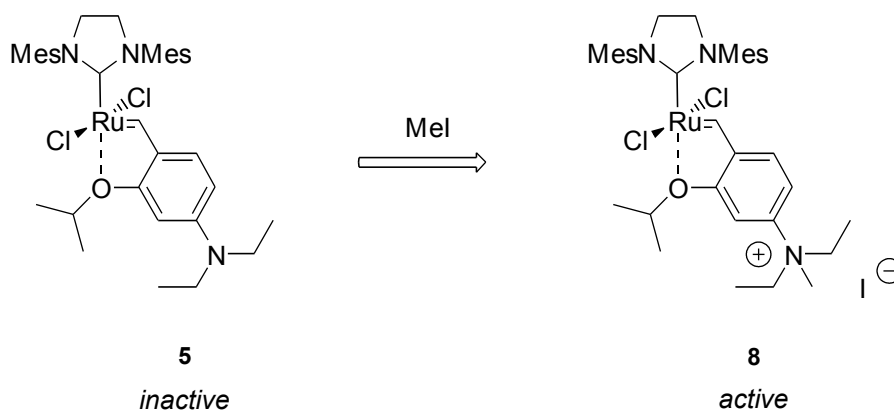


Figure 5: Complex **8** bearing a quaternary ammonium group.

I also designed an efficient new strategy for homogeneous Ru-catalyst phase-separation and recovery of catalyst which provide products of excellent purity before silica gel chromatography or distillation.

The new catalyst **7**^{12,17} exhibits a high affinity for silica when CH₂Cl₂ is used as solvent and can be easily eluted with ethyl acetate enabling its efficient removal (Figure 6). Importantly, crude organic products obtained after evaporation of a CH₂Cl₂ fraction possess relatively low content of residual ruthenium (typically below 400 ppm). Regenerated **7** can be used similarly to the pristine catalyst and this process can be repeated up to 8 times.

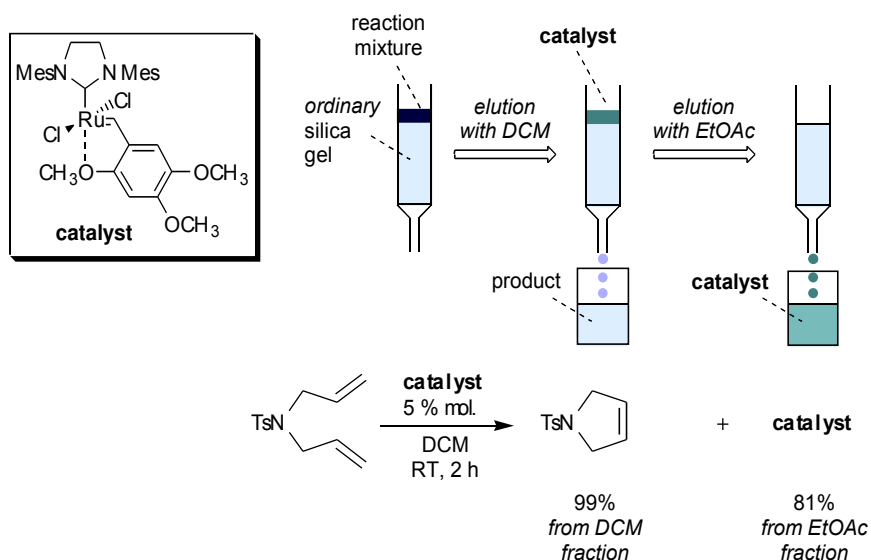


Figure 6. Phase-separation and catalyst **7** recovery experiment (5 mol % Ru) using ordinary silica gel.

In the second part of my research I focused on extending the scope of metathesis to unknown classes of compounds. Using the very active “nitro” catalysts **6a** and **6b** I examined CM reaction of α,β -unsaturated substrates such as: vinyl sulfones¹⁸ and vinylphosphine oxides.^{6g}

Functionalized vinyl sulfones are useful building blocks.¹⁹ Despite the CM reaction between simple terminal alkenes and phenyl vinyl sulfone is possible using second generation Grubbs catalyst, I have found that in the case of CM of more challenging alkenyl substrates more active “nitro” catalysts **6a** and **6b** had to be used.¹⁸ This transformation was later successfully applied by Evans in a stereoselective synthesis of (–)-maritolide and some other furanone natural products^{20a} and by Pyne in a formal synthesis of (–)-swainsonine.^{20b}

I have also demonstrated for the first time that vinylphosphine oxides could be successfully “dimerized” by catalytic olefin homo-metathesis leading to a series of new achiral and *P*-stereogenic diphosphine dioxides.²¹ It should be noted that examples of homometathesis between two electron-deficient olefins are considered to be very challenging.²²

Conclusion

During my Ph.D. study I have showed that the activity of ruthenium metathesis catalysts can be enhanced by introduction of electron-withdrawing groups without detriment to catalysts stability.⁹ This principle can be used not only to increase the catalyst activity, but also to alter its physical-chemical properties, such as solubility in given medium or affinity to silica gel.^{9,16} An example of novel immobilization strategy, based on this concept was presented. In fact, the possibility of reversibly binding catalysts to a solid phase is of major importance for industrial applications, particularly when continuous flow processes with immobilized homogeneous catalysts are pursued.

I have also demonstrated that various substituted chiral vinylphosphine oxides can be accessed by CM reaction of enantiopure phosphine oxides catalyzed by **6a** and **6b**. This reaction proceeds without any racemization of the chiral phosphorus center.

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