# Phase Tags in the Recycling of Homogeneous Grubbs Catalysts

Sumeng Liu Literature Seminar October 28th, 2014

Since they were first synthesized in 1992, the ruthenium catalyst named after Nobel Laureate R. H. Grubbs have become a useful tool in organic synthesis. Compared to conventional heterogeneous metathesis catalysts, Grubbs catalysts are more reactive, faster to initiate and better for reaction control.[1] Grubbs catalysts have been employed in good effort both in academia and industry, the later in the synthesis of certain pharmaceutical intermediates. [2] One variety of Grubbs catalyst, known as second generation Hoveyda-Grubbs Catalyst, contain N-heterocyclic carbene (NHC) ligands and chelating benzylidene ligands (**Fig. 1**). These second generation catalysts exhibit enhanced stability and reactivity.

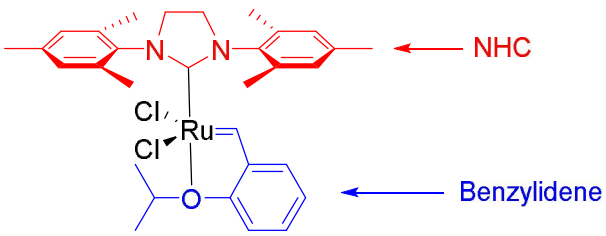


**Figure 1**. Second generation Hoveyda-Grubbs Catalyst

However, the separation and recycling of Grubbs catalyst from reaction system at a large scale remains difficult, as is often the case for homogeneous catalysis.In view of the high cost of ruthenium, the high catalyst loads used in large scale reactions and the requirement that the ruthenium content in pharmaceuticals be less than 10 ppm, there is a need to separate and recycle Grubbs catalysts. [3]

One approach to the separation and recycling of Grubbs Catalysts is to modify them with a functional group called “a tag” that can be used to “pick up” the catalyst from the reaction mixture. Tags that change the solubility of catalyst are referred to as phase tags. These tags enable the use of phase transfer catalysis and the use of non-lipophilic solvents, such as water, fluorocarbons and ionic liquids. In the past ten years, catalysts with fluorocarbons, polyether or ionic groups have shown some promise for improved catalyst recycling.

Here we review the use of Hoveyda-Grubbs Catalyst with ionic phase tags for Grubbs Catalyst recycling. Ionic groups are especially useful phase tags because of their affinity to non-lipophilic solvents and silica gel, the ease with which they can be modified to suit the need at hand and other factors. Second generation Hoveyda-Grubbs catalysts constitute an ideal platform for studying the effect of phase tags because of their high stability and their

reusability in ring-closing metathesis.

To decide where to put the tag, the mechanism of catalysis needs to be taken into account. In olefin metathesis, the benzylidene ligand will leave the catalyst during the catalysis cycle, whereas the other ligands do not. [4] As a result, tagging on different ligands will result in a different effect on ruthenium removal or catalyst recycling. Currently most tagging studies of Hoveyda-Grubbs catalysis recycling using ionic phase tags involve tagging the benzylidene ligand, because this approach enables easy separation of the active catalyst.

In 2003 and 2005, two groups synthesized first and second generation Hoveyda-Grubbs catalysts with ionic phase tags and investigated them in ionic liquid or biphasic systems **(Fig. 2)**. [5] The high viscosity of ionic liquids limits the diffusion rate, reduces the reaction rate and leads to difficulty in completely separating the product. Biphasic ionic liquid-organic solvent systems have lower viscosity thus enhanced the recyclability, but the limited reaction rate, the high cost of ionic liquids, and the contamination of organic products caused by incomplete extraction were still problematic.[6]

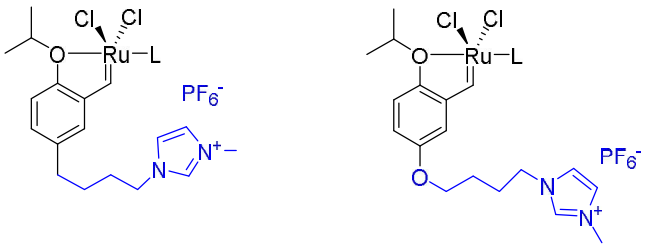


**Figure 2.** Hoveyda-Grubbs catalyst with ionic phase tags. L=$PCy_3$ (first generation) or NHC (second generation)

In order to overcome the side effects associated with non-lipophilic solvents, the concept of a switchable phase tag was introduced. A switchable phase tag is a tag that can change the solubility of the molecule upon stimulation with a trigger.[7] The trigger can involve stimuli such as irradiation with light or change in redox state. In 2010, Liu et al. synthesize a Hoveyda-Grubbs catalyst with a light-controlled phase tag, which exhibited some promising results.[6] Upon being triggered with light, the spiropyran converts to a charge separated merocyanine form (**Fig. 3**), making the catalyst no longer soluble in lipophilic solvents. The catalyst could then extracted into a hydrophilic solvent and subsequently converted back to the spiropyran form. The recovered catalyst was then extracted back into dichloromethane, leaving the decomposed catalyst in the hydrophilic phase, and completing a catalyst re-cycle. This method not only retains the reactivity of homogeneous Hoveyda-Grubbs catalyst, but also exhibits low ruthenium contamination and good recyclability.

To conclude, modifying homogeneous catalyst with a switchable phase tag is an attractive idea for homogeneous catalyst recycling. Considering the diversity of catalysts and solvents, this strategy could be further applied to the recycling of other expensive homogeneous catalysts.

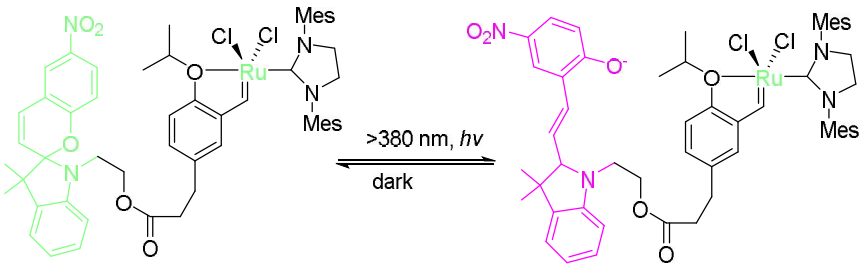


**Figure 3.** Switch between spiropyran form (left) and merocyanine form (right)


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