

Redox-Switchable Phase Tags for Recycling of Homogeneous Catalysts**

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Dedicated to Professor H. W. Roesky
on the occasion of his 70th birthday

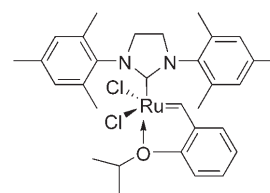
A fundamental problem of homogeneous catalysis is the difficulties associated with the recovery of the molecular catalyst after product formation, thus leading to loss of the catalyst and contamination of the reaction products with heavy-metal impurities.^[1,2] This problem is aggravated by the fact that increasingly sophisticated complexes with tailor-made ligands result in high-value catalysts. Consequently, numerous concepts have been tested to overcome the imminent problem of catalyst/product separation,^[3,4] such as soluble polymeric catalysts,^[5,6] biphasic solvent systems which involve various solvent combinations (namely, organic/organic,^[7] fluoruous/organic,^[8] ionic liquids/supercritical fluids,^[9] aqueous/organic^[10,11]), nanofiltration,^[12,13] incarcerated nanoparticles,^[14,15] interphase catalysts,^[16] supported liquid films,^[17] and immobilization of molecular catalysts on organic^[18] or inorganic supports.^[19]

Clearly, these approaches rely on manipulation of the solubility properties;^[20] most often, distinct solubility properties are imposed by so-called phase tags, such as sulfonate groups (in triphenyl phosphorothionates),^[21] fluoruous ponytails,^[8] or polar and nonpolar soluble polymers.^[22,23]

Such solubility-determining groups are referred to as phase tags and are an important tool in separation strategies.^[24] Despite the success of this approach, certain disadvantages of this concept are apparent. Clearly, two solvents are required in biphasic systems, one to hold the product and the other for the tagged catalyst complex. Both solvents need to be compatible with the catalytic reaction, their mutual solubility should be low, the leaching of the catalyst into the product-containing solvent has to be minimized, and the partition coefficient of the reactants/products needs to be in a suitable range. Alternatively, the tagged catalyst can be precipitated from the reaction solvent by addition of another solvent after the catalytic transformation. However, very large amounts of this second solvent are typically needed to effect the quantitative precipitation of the tagged catalyst.

To avoid these problems, we propose herein a strategy for the separation of homogeneous catalysts from the products of the reaction based on a new class of solubility-determining groups, which we term redox-switchable phase tags. In contrast to other phase tags, the solubility properties of redox-switchable phase tags can be altered through the employment of tag-centered reactions, thus resulting in drastic changes in the polarity of the respective solubility-determining group. In this manner, it should be possible to exert perfect control over the solubility behavior of catalysts^[25] by using a single solvent. We decided to utilize tag-centered redox reactions which mutate neutral (lipophilic) tags into charged (lipophobic) tags and back. One significant advantage of such an approach is that drastic changes in the solubility behavior can be effected with only very small amounts of switching reagent, which is stoichiometric with respect to the catalytic amounts of catalyst complex present in a reaction mixture.

To illustrate this principle, we chose a ruthenium-based catalyst of the Grubbs–Hoveyda type for olefin metathesis as numerous recycling concepts have been tested on these high-value catalysts because of their effectiveness.^[26–32] Prior to the synthesis of a modified olefin-metathesis catalyst of the Grubbs–Hoveyda type with redox-switchable tags, a suitable redox-active group needed to be found. We chose a ferrocene (Fc) unit because such metallocenes are well-behaved outer-sphere redox reagents that display a high degree of reversibility. Furthermore, the redox potential of the ferrocene unit can be varied readily over a large potential range through the attachment of different substituents on the cyclopentadienyl rings,^[33] which is clearly a very important property as the redox potential of the redox tag must be fine-tuned to avoid electron-transfer reactions that involve the catalytically active metal center. The Fe^{II}/Fe^{III} redox couple of the ferrocene unit should differ by between 236 mV (ratio of Fe/Ru oxidation = 100:1) and 354 mV (1000:1) from that of the olefin-metathesis catalyst to be useful. Thus, the Ru^{II}/Ru^{III} redox potential of the Grubbs–Hoveyda catalyst was first established by cyclic



Grubbs–Hoveyda catalyst

voltammetry (CV). The CV waves are well behaved, that is, they are fully reversible and the redox potential was +0.85 V in CH₂Cl₂ (Figure 1). As the redox potential of ferrocene itself is +0.46 V under the same conditions, we conclude that any ferrocene compound with electron-donating substituents can undergo independent Fe^{II}/Fe^{III} redox reactions that do not interfere with the catalytically active Ru^{II} center.

The synthesis of a ferrocenyl-tagged olefin-metathesis catalyst is shown in Scheme 1. We chose a monoalkylated ferrocene as the redox tag, as its redox potential fulfils the

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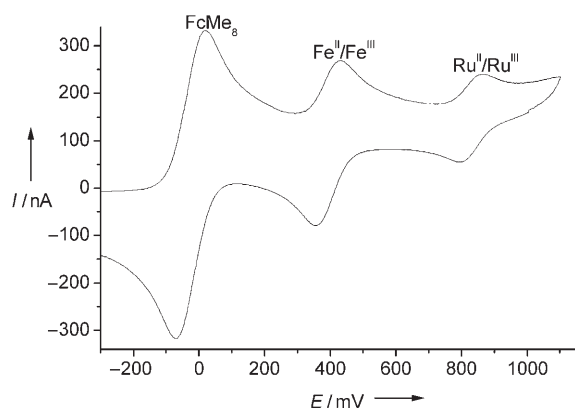
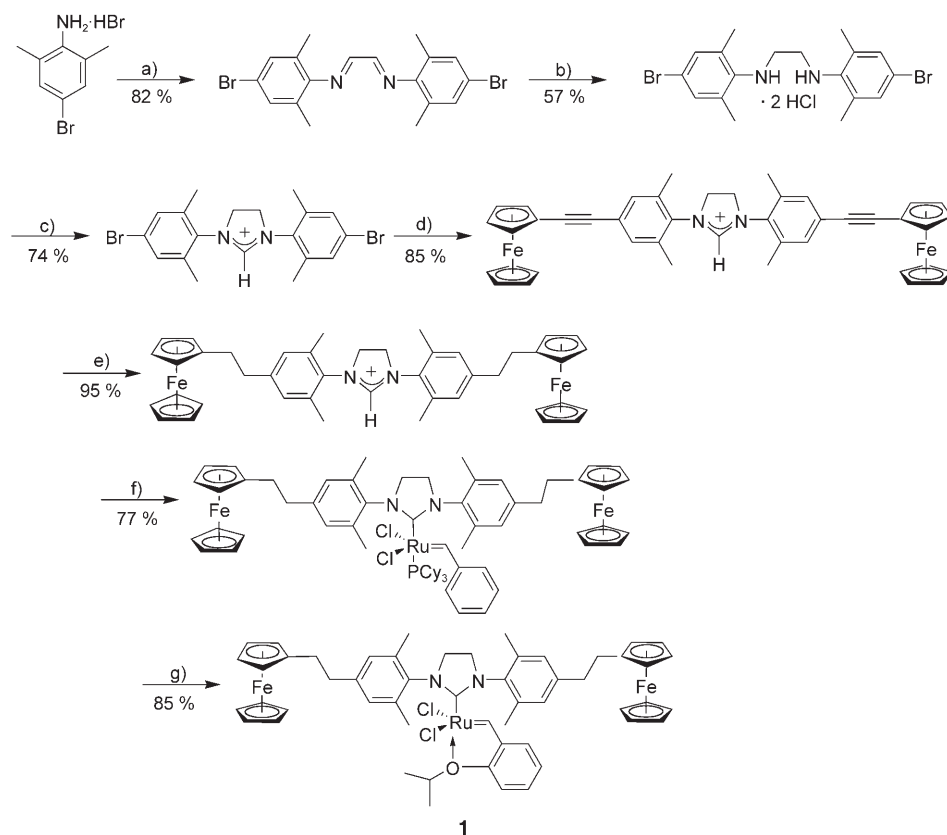


Figure 1. Cyclic voltammogram of the diferrocenyl-tagged Grubbs-Hoveyda-type catalyst **1**. $\Delta E_{1/2}$ ($\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$) = +0.410 V (70 mV), $\Delta E_{1/2}$ ($\text{Ru}^{\text{II}}/\text{Ru}^{\text{III}}$) = +0.847 V (60 mV) referenced versus FcMe_8 (−0.010 V) in CH_2Cl_2 .



Scheme 1. Synthesis of the ferrocenyl-tagged olefin-metathesis catalyst **1** of the Grubbs-Hoveyda type: a) NEt_3 , EtOH, HCOOH , 24 h; b) 1. LiAlH_4 , THF; 2. HCl ; c) $\text{HC}(\text{OEt})_3$, 130°C , 24 h; d) FcCCH , Na_2PdCl_4 , CuI , $\text{Ad}_2\text{PBn-HBr}$, DMSO, HNiPr_2 , 80°C , 24 h; e) Pd/C 5 bar H_2 , 5 h, RT; f) KOtBu , Grubbs I catalyst, toluene, THF; g) 2-isopropoxystyrene, CuCl , CH_2Cl_2 , 40°C , 1 h. Cy = cyclohexyl, Ad = adamantyl, DMSO = dimethyl sulfoxide.

criteria defined above. 4-Bromo-2,6-dimethylaniline was treated with glyoxal to give the respective 1,2-diimine in 75% yield, which was reduced to the corresponding 1,2-diamine in 80% yield using LiAlH_4 . Ring-closure with $\text{HC}(\text{OEt})_3$ yielded the respective imidazolium salt in 75% yield. For the introduction of the redox tag, the aryl bromide

functionalities of this salt underwent Sonogashira coupling to ferrocenyl acetylene, thus giving the coupled product in 85% yield. It should be noted that the reaction conditions for the Sonogashira coupling are critical: First, the imidazolium chloride displays solubility only in a few polar solvents, and second, the number of suitable bases is rather limited because the competing deprotonation of the imidazolium ring must be suppressed as the corresponding N-heterocyclic carbene appears to inhibit the Pd catalyst.

Next, the acetylene linker was reduced with H_2 over Pd/C to the $-\text{C}_2\text{H}_4-$ bridge in almost quantitative yield. The reason for this transformation is threefold: 1) an alkyl substituent attached to the ferrocene unit is electron donating rather than electron withdrawing, which consequently leads to an increase in the difference in the redox potential between the $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ and $\text{Ru}^{\text{II}}/\text{Ru}^{\text{III}}$ redox couple; 2) the hydrogenation of the acetylene linker electronically decouples the redox-active ferrocene group from the catalytically active center to avoid any undesired influence of the ferrocene cation on the catalytically active center after oxidation; 3) the absence of a triple bond avoids potential problems in olefin metathesis.

Finally, the imidazolium cation is deprotonated with KOtBu and treated with the Grubbs I catalyst; subsequently, the remaining PCy_3 ligand and the benzylidene in the resulting complex are substituted with 2-isopropoxystyrene to yield the desired redox-tagged Grubbs-Hoveyda-type catalyst **1**.

The catalytic properties of **1** are demonstrated in the ring-closing metathesis (RCM) reaction of *N*-tosyldiallylamine (Figure 2). The unperturbed reaction (●) proceeds to completion exactly as expected for such catalysts. In a second run (■), a solution of two equivalents of oxidation reagent ($[\text{FcCOCH}_3][\text{CF}_3\text{SO}_3]$ as a 10% solution in 0.1 mL of CH_2Cl_2 ($\Delta E = +0.73$ V)) with respect to the catalyst was added after exactly 60 minutes. The two ferrocenyl tags were oxidized virtually instantaneously, and the resulting dication **1**²⁺ precipitates from the solution of toluene within a few seconds. The precipitated catalyst does not display significant catalytic activity, as can be seen in the plot of conversion versus time (Figure 2, ■). The product of the catalytic reaction can be readily separated from the pre-

cipitated catalyst by filtration, which is preferably done after completion of the reaction. The catalyst can be reactivated (namely, redissolved) at any time by addition of two equivalents of a reducing agent (1,1',2,2',3,3',4,4'-octamethylferrocene (FcMe_8)), which was carried out after 135 minutes in our experiment. It can be seen that the catalytic activity is

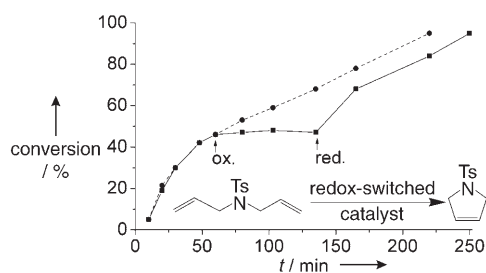


Figure 2. Switching of the olefin-metathesis catalyst **1** in toluene, monitored by GC: unperturbed RCM (●), off/on switched RCM (■). Ox. and red. denote the respective oxidation and reduction of the redox tag with $[\text{FcCOCH}_3][\text{CF}_3\text{SO}_3]$ and FcMe_8 . Ts = *p*-toluenesulfonyl.^[35]

immediately restored to its initial value and the reaction proceeds to completion (not shown in Figures 2 and 3).^[34]

Following this procedure, the catalyst can also be switched off and on^[36,37] several times after completion of the RCM reaction, thus allowing multiple recycling of the catalyst. We tested redox-switching of the phase tag for three consecutive reaction cycles composed of 1) olefin metathesis, 2) oxidation with an acetyl ferrocene cation, 3) precipitation and separation, and 4) reduction and redissolution of the catalyst, and we observed quantitative yields for all the reaction steps. We probed the identity of the recycled catalyst after a single oxidation/reduction sequence $\mathbf{1} \rightarrow \mathbf{1}^{2+} \rightarrow \mathbf{1}$ and identified the initial Grubbs–Hoveyda-type catalyst **1** by ^1H NMR spectroscopy.

Furthermore, it is also possible to adjust the rate of the catalytic transformation as desired by reversible precipitation of a limited amount of the catalyst after addition of substoichiometric amounts of the oxidation reagent. Although the curve denoted by ■ in Figure 3 displays a single off/on switching event, the double-switched RCM reaction in the curve denoted by ● shows an off/on switching event during the first 30 minutes and a partial-off event after 50 minutes, with a full restoration of catalytic activity after 75 minutes.

Instead of monitoring the switching events by gas-chromatographic or NMR spectroscopic analysis, the removal of the catalyst from the solution can be followed readily by

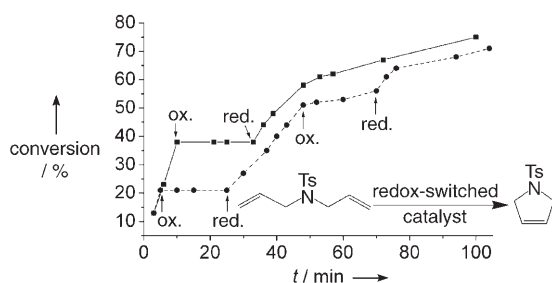


Figure 3. Switching of the olefin-metathesis catalyst **1** in C_6D_6 , monitored by ^1H NMR spectroscopy: single-switch RCM (■), off/on/partially-off/on switched RCM (●). Ox. = oxidation and red. = reduction for the redox tag with $[\text{FcCOCH}_3][\text{CF}_3\text{SO}_3]$ and FcMe_8 , respectively. Two equivalents of the oxidant were added to switch off the catalyst and one equivalent to partially switch off the catalyst.

monitoring the UV/Vis spectrum of the reaction mixture; catalyst **1** is characterized by a strong Ru-centered absorption band at 375 nm, the intensity of which reflects the concentration of the catalyst in solution.

As an alternative to chemical redox switching, which requires stoichiometric amounts of redox reagent (only with respect to the catalyst), electrochemical triggering of the tag switching only requires an applied current. Ideally, the catalyst is electrodeposited on the surface of an electrode on oxidation and is redissolved on application of a reductive potential. In this manner, the transfer of the loaded electrode from a solution containing the product into a solution containing fresh reactants allows efficient reuse of the catalyst. For the coulometric deposition of a redox-tagged catalyst, solvents are needed that display a reasonable conductivity after addition of supporting electrolytes. Consequently, electrolysis in toluene is not possible as the currents observed are far too small to effect electrolysis within a reasonable time frame, and so slightly more polar solvents are required. We tested a number of solvents of intermediate polarity and were able to quantitatively oxidize **1** electrochemically. However, the minute concentrations of catalytically active dication used for the RCM reactions are soluble in solvents of intermediate polarity (e.g., CH_2Cl_2). Therefore, the synthesis of new catalysts with multiple redox tags is required to solve these problems.^[38]

In conclusion, we have demonstrated that redox-switchable phase tags, whose solubility properties are controlled by redox reagents or electrochemical redox processes, can be used to effectively switch the catalytic activity of an olefin-metathesis catalyst of the Grubbs–Hoveyda type on and off. More importantly, this approach allows the efficient separation of such catalysts from the products of a catalytic reaction at any time during the reaction and after its completion. We expect the principle of redox-switchable phase tags to become a general concept for control over solubility properties and, consequently, the recyclability of a wide variety of homogeneous catalysts. We are currently working towards the application of this principle several to other types of homogeneous catalytic processes, such as enantioselective hydrogenation and various Pd-mediated cross-coupling reactions.

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- [34] Dynamic phase-tag switching of **1**: Diallyltosylamide (25 mg, 0.1 mmol) was added to a solution of **1** (0.8 mg, 1 mol %) in toluene (10 mL), and the reaction mixture was warmed to 35 °C. After 3 h, the solution was cooled to room temperature with subsequent addition of [FcCOCH₃][BF₄] (2 equiv) in CH₂Cl₂ (200 mL; *c* = 0.01 mol L⁻¹) to oxidize/precipitate **1**²⁺. The solution was filtered over cotton wool, and the volatiles were evaporated to obtain the crude product. The cotton wool was rinsed with CH₂Cl₂ (0.5 mL) to dissolve **1**²⁺, which was subsequently treated with a solution of FcMe₈ (2.1 equiv) in toluene (300 mL; *c* = 7.0·10⁻³ mol L⁻¹) to regenerate **1**. After addition of fresh toluene (10 mL) and diallyltosylamide (25 mg, 0.1 mmol), a new reaction cycle was started. The whole procedure was repeated three times, and quantitative product formation was observed after each cycle. The switching on/off of catalyst **1** during the reaction was carried out by addition of solutions of [FcCOCH₃][BF₄] (**1**→**1**²⁺ = off) and FcMe₈ (**1**²⁺→**1** = on) as oxidizing and reducing agents, respectively. Spectroscopic data of **1**: ¹H NMR (500 MHz, C₆D₆): δ = 1.37 (d, 6H, *J* = 6.0 Hz, (CH₃)₂CHOAr), 2.61 (bs, 12H, *ortho*-CH₃), 2.73 (m, 4H, CH₂), 2.86 (m, 4H, CH₂), 3.47 (s, 4H, NCH₂CH₂N), 4.03 ("t", 4H, *J* = 1.8 Hz, FcH), 4.09 (s, 10H, FcH), 4.12 ("t", 4H, *J* = 1.8 Hz, FcH), 4.52 (sept, 1H, *J* = 6.2 Hz, (CH₃)₂CHOAr), 6.35 (d, 1H, *J* = 8.3 Hz, sp² CH), 6.73 (t, 1H, *J* = 7.4 Hz, sp² CH), 7.05 (s, 4H, *meta*-CH), 7.10 (m, 1H, sp² CH), 7.20 (dd, 1H, *J* = 7.6, 1.6 Hz, sp² CH), 16.74 ppm (s, 1H, RuCHAR); ¹³C NMR (125.75 MHz, C₆D₆): δ = 19.5, 20.2, 29.5, 36.6, 50.0, 66.4, 67.1, 67.6, 73.7, 87.5, 111.9, 120.7, 121.1, 123.2, 127.7, 142.0, 144.5, 151.3, 211.6, 293.5 ppm.
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