CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201002014

Dendrimer-Induced Molecular Catalysis in Water: The Example of Olefin Metathesis

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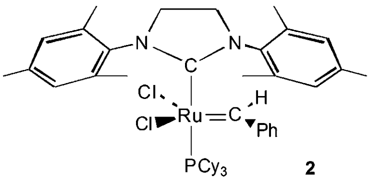
Metallodendritic catalysis, in which the molecular catalyst is covalently attached to the core or periphery of the dendrimer, is a well-developed research area.[1] A dendrimer can also provide a radial polarity gradient suitable for organocatalysis, and this principle was shown by Fréchet's group to accelerate the intradendritic dehydrohalogenation of 2-iodo-2-methylheptane, proceeding with E^1 elimination mechanism, and $^1O_2$-sensitized peroxidation reactions.[2] Another remarkable case is that of dendrimer-encapsulated palladium nanoparticles for which Crooks et al. showed that dendrimer encapsulation of such nanoparticle catalysts provides selectivity, the dendrimer playing the role of an efficient "nanofilter".[3] Catalysis by dendrimer-encapsulated molecular transition-metal catalysts is still unknown, however. Yet, the function of dendrimers as unimolecular micelles has been pioneered by Newkome in his seminal publication on "arborols",[4] and Tomalia and other groups have also shown useful dendrimer encapsulation of guest molecules in early works.[5,6]

Therefore one can envisage that common and commercial catalysts could be temporarily encapsulated inside dendrimers at the same time as substrates for intradendritic catalysis. Application of this idea could be beneficial for catalysis in pure water, a challenging topic. For this purpose, the dendrimer should be water-soluble and at the same time be capable of encapsulating hydrophobic compounds in its hydrophobic interior. Polyethyleneglycols (PEGs) are adequate for the decoration of the dendrimer periphery, because they insure the water solubility of dendrimers and are also compatible with hydrophobic compounds. Indeed, Fréchet's group, followed by many others, showed that PEG-terminated dendrimers could encapsulate various hydrophobic drugs for medical applications.[7] Very recently, this group has also reported a family of enzyme-inspired polymer catalysts from modular star polymers.[8]

Various efficient, water-soluble, ruthenium–benzylidene olefin, metathesis catalysts[9] for metathesis of water-soluble olefins in homogeneous water have been reported, in particular by Grubbs and by Grela,[10,11] and metathesis of hydrophobic olefins in water mixed with another solvent is also known.[12] In some cases, olefin metathesis of hydrophobic substrates has also been reported in pure water,[13–15] including with the use of ultrasonification[14] or surfactants.[15] This field is thus the subject of fast-growing attention.[11]

We now report catalysis of ring-closing metathesis (RCM), cross metathesis (CM) and enyne metathesis (EYM), in water and air under ambient or mild conditions using low catalytic amounts (0.083 % mol) of a suitably designed dendrimer **1** (that can be re-used many times), and of Grubbs' second-generation olefin-metathesis catalyst [Ru(=CHPh)Cl$_2${1,3-bis(mesityl)-NHC}(PCy$_3$)] (**2**, NHC = 4,5-dihydroimidazolin-2-ylidene; so-called "Grubbs-II"[9]).



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The new dendrimer **1** was synthesized by [Fe(η^5-C$_5$H$_5$)]$^+$-induced nona-allylation of mesitylene, followed by photolytic removal of [Fe(η^5-C$_5$H$_5$)]$^+$,[16] hydrosilylation with chloromethyldimethylsilane, chloride/azide substitution to give a known dendritic core,[17] and continuation of the 1→3 connectivity[4] upon "click" reaction with a Percec-type dendron[18] functionalized at the focal point with a propargyl group and on the periphery with triethyleneglycol tethers (Scheme 1; see the Supporting Information for the experimental details of the synthesis, the ^{1}H and ^{13}C NMR spectra and the MALDI TOF mass spectrum). The dendrimer **1** was

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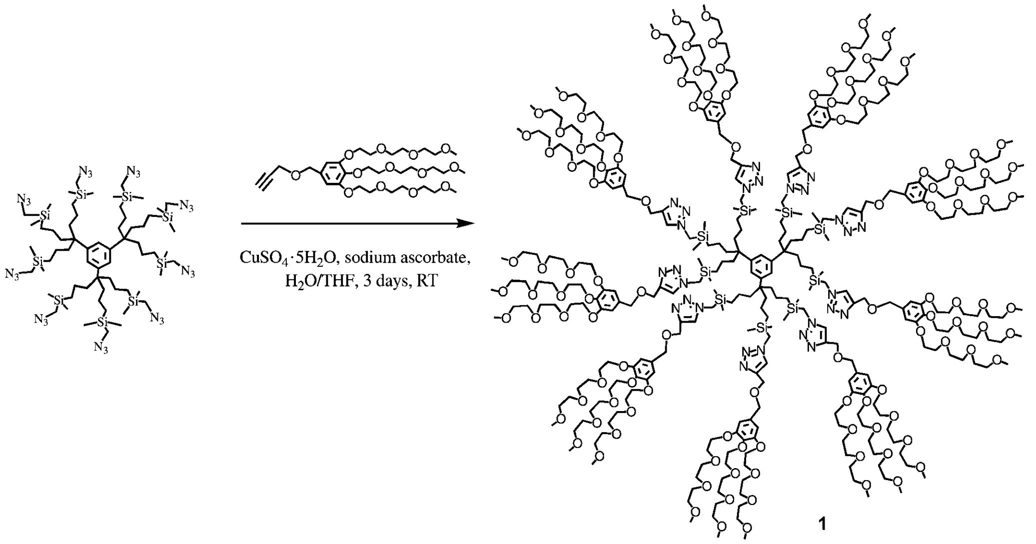
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002014.



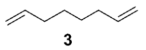
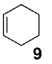
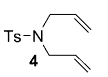
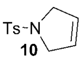
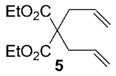
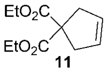
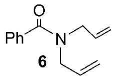
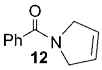
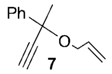
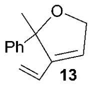
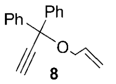
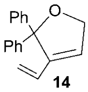
Scheme 1.

characterized in particular by the appearance of the 1,2,3-triazole proton at 7.45 ppm in the ^{1}H NMR spectrum recorded in $CDCl_3$, the disappearance of the alkyne and azide bands in the IR spectrum, the molecular peak at 7234.1 ($[M+Na]^+$) as the dominant peak in the MALDI TOF mass spectrum (calcd for $C_{342}H_{597}O_{117}N_{27}Si_9$: 7212.2), and correct elemental analysis (calcd C56.95, H8.34; found: C56.37, H8.33). Size exclusion chromatogram consistently showed a fully symmetrical elution band (see the Supporting Information). The DOSY ^{1}H NMR experiment provided a diffusion coefficient $D = 1.36\ (\pm 0.1) \times 10^{-10}\ m^2 s^{-1}$ that led to a hydrodynamic diameter of 5.54 ($\pm$0.2) nm for **1** using the Stokes–Einstein equation, and considering **1** as a sphere (see the Supporting Information).

Among the commercial Ru–benzylidene metathesis catalysts probed in this system (see the Supporting Information), the most successful catalyst under these conditions is **2**. Using only water as the solvent in the presence of the water-soluble dendrimer **1** (less than 0.1 % mol vs. substrate), only 0.04 % of **2** leads to the RCM of **4** giving **10** with 62 % conversion at 25 °C; 2 % of **2** is required under the same conditions for CM and EYM with 97–99 % conversions (Table 1 and the Supporting Information). For electron-deficient olefins, the CM reactions are found to be stereoselective, but require heating to 40 °C (Schemes 2 and 3). The yields of the isolated CM reaction products **17** and **19** under these conditions are 66 and 83 %, respectively, but drop to 10 and 17 %, respectively, in the absence of the dendrimer **1**.

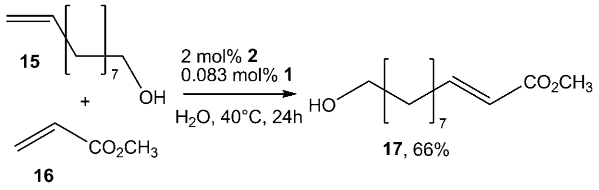
Besides the fact that these reactions are carried out in pure water and air under mild conditions, another remarkable feature is that extremely low loading of **2** is used for RCM. Indeed, the RCM reactions usually provide conversions and yields around 90 %, with only 0.1 % catalyst **2** (Table 1, entries A–D). We do not find very significant differences between reactions carried out under N_2 and those in air (for instance, 60 % conversion in air vs. 66 % conversion under N_2, using 0.06 mol % **2**) despite a color change of the reaction from off white to dark beige in air unlike for reactions carried out under N_2.

Table 1. Ring-closing metathesis reactions using Grubbs second-generation catalyst **2** and dendrimer **1** in H_2O and air at 25 °C for 24 h.

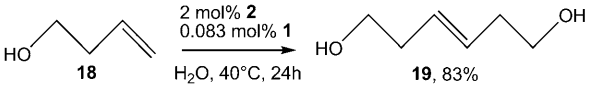
	Substrate	Product	Cat. **2**[a] [mol %]	Conv. [%] without **1**	Conv. [%] with 0.083 % **1**
A	 **3**	 **9**	0.1	0	86[b]
B	 **4**	 **10**	0.1	0	90[c]
			0.06	0	66[c]
			0.04	0	62[c]
C	 **5**	 **11**	0.1	6[b]	89[b]
D	 **6**	 **12**	0.1	0	90[c]
E	 **7**	 **13**	2	27[c]	97[c]
F	 **8**	 **14**	2	30[c]	99[c]

[a] The % mol of the Ru catalyst **2** in this column are vs. substrate; for instance 4 mg of **2** dispersed in 47 mg of water corresponds to 0.1 % mol **2**, vs. substrate. The dendrimer amount of 0.083 % mol vs. substrate corresponds to 28 mg of **1**, that is, 83 μmol L^{-1} (see the Experimental Section). [b] The reaction mixture without the catalyst was analyzed by ^{1}H NMR spectroscopy in $CDCl_3$, following filtration of the Ru catalyst or resulting residual species, then extraction with diethyl ether [c] The reaction mixture without the catalyst was analyzed by GC (injection of the extracted diethyl ether solution, see the Supporting Information).

We have verified that the reactions do not yield significant amounts of RCM products in the absence of the den-



Scheme 2.



Scheme 3.

drimer **1** under our reaction conditions (see Table 1). For EYM with 2 % of catalyst **2**, the conversions decrease from 97–99 % in the presence of 0.083 % mol of dendrimer **1** to 27–30 % in the absence of dendrimer.

As shown earlier, RCM reactions can proceed in the presence of water even without surfactant, but the amount of first- or second-generation Grubbs catalyst required then reaches 4 to 5 % for good- to high-yield reactions,[13] which is of the order of 100 times more ruthenium catalyst than under our reaction conditions. We have indeed verified that these literature results are reproducible with **2**.[13b]

Finally, the last key feature of the present system is that the aqueous solution of the water-soluble dendrimer **1** can be recycled, because **1** is insoluble in diethyl ether. Re-use of the aqueous solution of **1** can be carried out subsequent to filtration of the water-insoluble catalyst after the reaction and removal of the organic reaction product by decantation or extraction with diethyl ether. Remarkably, we have been able to recycle this aqueous dendrimer solution at least ten times without any significant yield decrease (see Table 2).

Table 2. Recycling the aqueous solution of dendrimer **1** with the use of 0.1 mol % Grubbs-II catalyst **2** for the RCM of **4**.[a]

Cycle number	1	2	3	4	5	6	7	8	9	10
conversion [%, ±3 %]	90	89	87	86	87	87	86	86	86	85

[a] The catalyst **2** was not recycled, given the low amount of 0.1 mol % **2** (4 mg) used for each experiment. See Table 1, entry B for the lower limit of the % mol **2** vs. **4** (0.04 %). Conversions were determined by GC (see the Experimental Section and the Supporting Information).

The reaction mixtures are heterogeneous in these systems, that is, **2** is in equilibrium between the solid state and the dendrimer-solubilized state (Scheme 4).

$$[L_nRu{=}CHPh]_{solid} \rightleftharpoons [L_nRu{=}CHPh]_{dendrimer}$$

Scheme 4.

The catalyst **2** looks insoluble under the reaction conditions. Physical data do not permit us to establish the presence of the Ru catalyst inside the dendrimer, although such a transitory situation is likely for minute amounts of **2** in view of the marked property of dendrimers to encapsulate various kinds of substrates.[2–6] The driving force for the interaction of the hydrophobic catalyst **2** and substrates is their hydrophobicity matching the hydrophobic dendrimer interior. Note that the required amount of catalyst to reach high conversions is very low compared to metathesis reactions carried out in (or "on") various solvents including water (vide supra). It is especially intriguing that high amounts of ruthenium catalyst are required to carry out RCM reactions in the presence of water in the absence of the dendrimer, which means that the catalyst eventually undergoes some decomposition in water in competition with RCM of terminal olefins. Thus, we have tested the stability of the Grubbs-II catalyst **2** in the presence of water at ambient temperature for 24 h, and found that it is stable in the absence of olefin substrate. For instance, after stirring 0.1 % mol **2** in suspension in water for one day at 25 °C in air, the substrate **4** and the dendrimer **1** were then added and, after an additional day, the results of the RCM reaction were not significantly changed (80 % conversion) compared to the result indicated in Table 1, entry B (90 % conversion) under the same conditions. This means that the pre-catalyst **2** itself is stable and that the relative instability of **2** during metathesis in the presence of water (but in the absence of dendrimer **1**) is due to the slow decomposition of the catalytically active species formed during the RCM catalytic cycle. In particular, it has been shown that the methylene species $[Ru(=CH_2)Cl_2\{1,3\text{-bis(mesityl)-NHC}\}(PCy_3)]$, generated in the catalytic cycle of RCM reactions involving terminal olefins, is usually highly subject to dimerization and decomposition in CH_2Cl_2 or C_6H_6.[9] Whatever be the decomposition path of this species in the presence of water, it appears that such a decomposition is considerably reduced when the dendrimer **1** is used for the RCM reactions. This strongly argues in favor of a dendritic protection (probably by encapsulation) of this reactive species. RCM reactions need lower amount of catalyst **2** in organic solvents[9] than in the presence of water, especially in the absence of the dendrimer **1**. Thus the hydrophobic dendrimer interior should indeed be favorable to protect this intermediate ruthenium–methylene species from side reactions occurring in the presence of water.

In conclusion, we have disclosed extremely efficient RCM metathesis reactions with the commercial Grubbs-II catalyst **2** with high conversions and yields using only 0.1 % catalyst and 0.083 % of the new dendrimer **1** in pure water and air at 25 °C without significant yield decrease in air, compared to reactions under N_2. Under these conditions, the RCM reactions do not significantly proceed in the absence of the dendrimer **1**. The use of the water-soluble dendrimer **1** allows us to decrease the amount of this commercial ruthenium catalyst needed to carry out olefin RCM reactions in (or "on") water by a factor of the order of 100. Other metathesis reactions such as EYM and CM, which were also carried out in pure water and air with 2 % Grubbs catalyst **2**, also largely benefit from the presence of less than 0.1% mol of the dendrimer **1**. The dendrimer plays a protecting role toward catalytically active species involved in the metathesis catalytic cycle, preventing catalyst decomposition in the presence of olefin substrate. Moreover, this aqueous solution of dendrimer can be recovered and reused at least ten times without significant decrease of metathesis product yield. This strategy might in principle be extended to other types of catalysis, and research along this line is ongoing in our laboratory.

Experimental Section

Grubbs second-generation catalyst **2** (4 mg, 4.71 µmol, 0.1 mol% vs. **4**), the substrate **4** (1.184 g, 4.71 mmol), the dendrimer **1** (28 mg, 3.9 µmol, 83 μmolL^{-1}, that is, 0.083 mol% vs. **4**, 83 mol% vs. **2**), and distilled water (47 mL) were introduced into an Erlenmeyer flask, and the resulting heterogeneous reaction mixture was allowed to stir vigorously at 25°C for 24 h under air. Then, the insoluble ruthenium catalyst **2** was separated over a 0.22 µm millipore filter (PTFE). The product **10** was then extracted from the reaction mixture with diethyl ether, and analyzed by GC (a sample of this diethyl ether phase of the reaction mixture was directly injected), which provided a 90% conversion to **10**. The ether solvent was also removed under vacuum for ^{1}H NMR analysis in $CDCl_3$. The dendrimer, which is insoluble in diethyl ether, remained in the aqueous phase. This aqueous solution of **1** could be re-used with the present procedure at least ten times without any significant yield decrease for an analogous reaction (see Table 2 and the Supporting Information). On a 1.0 g scale of **4** (4 mmol), the yield of the RCM reaction of **4** using the same procedure was 87% (0.773 g, 3.5 mmol) after column chromatography on silica gel by using pentane/ethyl acetate 9:1. The same experiment in the above conditions, but carried out in the absence of dendrimer **1**, gave 0% conversion, and **4** was recovered. The procedure for the RCM reactions of **3**, **5**, and **6** (entries A, C, and D of Table 1) were identical. The same procedure was used with 2 mol% of **2** for EYM of **7** and **8** at 25°C giving **13** and **14**, respectively (entries E and F, respectively, of Table 1) and CM of **15** and **18** at 40°C giving **17** and **19**, respectively (Schemes 2 and 3, respectively, see the SI). The detailed experimental procedure for the synthesis of the dendrimer **1** including all characterizations and spectra is provided in the Supporting Information.

Acknowledgements

Financial support from the IUF, the Université Bordeaux 1, the CNRS and the ANR (project ANR-07-CPD-05-01) are gratefully acknowledged.

Keywords: dendrimers · Grubbs catalyst · heterogeneous catalysis · metathesis · water chemistry

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Received: July 16, 2010