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A Materials Approach to Site-Isolation of Grubbs Catalysts from Incompatible Solvents and *m*-Chloroperoxybenzoic Acid

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Abstract: The development of a method for site-isolation of Grubbs second-generation catalyst from MCPBA is described. In these reactions, Grubbs catalyst was dissolved in a solvent consisting of a mixture (1:1 v/v) of 1-butyl-3-methylimidazolium hexafluorophosphate and methylene chloride and completely encapsulated within a thimble fabricated from polydimethylsiloxane (PDMS). A series of molecules that react by cross metathesis or ring-closing metathesis were added to the interior of the thimble and allowed to react. In the last step, *m*-chloroperoxybenzoic acid (MCPBA) dissolved in MeOH/H_2O (1:1 v/v) was added to the exterior of the PDMS thimble. Small organic molecules diffused through the PDMS to react with MCPBA to form epoxides, but the Grubbs catalyst remained encapsulated. This result is important because Grubbs catalyst catalytically decomposes MCPBA at ratios of MCPBA to Grubbs of 3000 to 1. The yields for this two-step cascade sequence ranged from 67 to 83%. The concept behind this sequence is that small organic molecules have high flux through PDMS but large molecules—such as Grubbs catalyst—and ionic reagents—such as MCPBA—have much lower flux through PDMS. Small molecules can thus react both outside and inside PDMS thimbles, whereas incompatible catalysts and reagents remain site-isolated from each other. This method does not require alteration of structures of the catalysts or reagents, so it may be applied to a wide range of homogeneous catalysts and reagents. To demonstrate further that the catalyst was encapsulated, the Grubbs catalyst was successfully recycled within the cascade sequence.

Keywords: cascade reactions · epoxidation · metathesis · recycling

Introduction

The capability to carry out multiple reactions in one flask is an important goal in chemistry because of the need to speed the synthesis of molecules while producing less waste and requiring fewer hours of effort.[1–38] These reactions are often called cascade or domino reactions; their names refer to how several reactions occur in a predicted sequence in the same reaction vessel. These reactions are terrific examples of green chemistry because they require less solvent and produce less waste than the traditional method of isolating and characterizing products after each reaction.[5,30,39] Numerous cascade reactions have been developed, and many of them use one catalyst that catalyzes multiple steps, such as in a recent report in Nature of a catalytic reaction with a proline derivative to form four stereocenters in one pot.[1] The use of single catalysts to carry out multiple reactions has been very successful, but these cascade reactions typically require the development of new catalysts and cannot be integrated with numerous homogeneous catalysts that are often commercially available and are excellent catalysts for one reaction.[3] The main reason for this limitation is that these catalysts often poison one another or are poisoned by reagents required by a second catalyst. Thus, only one can be added to a reaction vessel, and no cascade sequence is possible. What is needed to advance the field of cascade reactions is a new method to integrate multiple catalysts and reagents to take advantage of mature homogeneous catalysts that catalyze one reaction very well.

Because many catalysts and reagents poison one another, they must be site-isolated from each other, such that multiple catalysts or reagents can be integrated into one reaction vessel for cascade reactions.[28,40–42] Site-isolation involves

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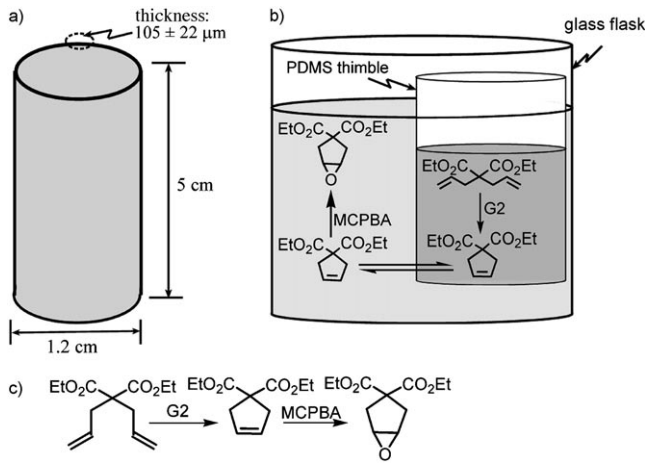
modifying the catalysts or reagents such that they do not come into contact and poison one another. Numerous methods for site-isolation exist, such as attachment to a polymer backbone, attachment of a catalyst to a solid polymeric support, attachment of catalysts to a heterogeneous surface, trapping a catalyst inside a zeolite cage, or using catalytic enzymes in which the active sites are protected by the enzyme from interacting with the active site of another enzyme.[10,17,20,43–60] These methods have been very successful in some instances: for example, Fréchet and Hawker attached both acidic and basic residues to the interiors of star polymers to integrate acid- and base-catalyzed reactions in one vessel.[48,49] In another example, heterogeneous acidic and basic clays were added to the same reaction vessel to carry out concurrent acid- and base-catalyzed reactions.[61] One critical limitation that hinders development of this approach is that most methods for site-isolation require the structure of the catalyst be altered for attachment to a polymer or solid support. These alterations may require several synthetic steps and affect the reactivity and selectivity of catalysts, or may simply not be possible with a wide variety of reagents. In this paper we report a simple method for site-isolation of a homogeneous, organometallic catalyst from a reagent through the use of a polymeric membrane. This method does not require the structures of the catalyst or reagent to be altered and will, we believe, be a general method for site-isolation of a variety of catalysts and reagents without affecting their structures.[62]

Our method for site-isolation of catalysts and reagents uses polydimethylsiloxane (PDMS) thimbles (Scheme 1). To begin this work, hollow PDMS thimbles 1.2 cm in diameter and 5 cm in height and with PDMS walls that were 105 μm thick were constructed. The bottoms of these thimbles were composed of PDMS, but the tops were left open for easy filling with solvent and catalyst. The concept behind the work in this paper is simple: the Grubbs catalyst was added to a solvent in the interiors of the PDMS thimbles and MCPBA to the exteriors of the thimbles. The Grubbs catalysts and MCPBA poison each other even at low loadings of the Grubbs catalyst, but they were site-isolated by the PDMS walls, whereas small molecules readily diffused through the walls to react with the catalyst and reagent. Cascade reactions with the Grubbs catalyst and MCPBA were therefore possible even though these molecules were vastly incompatible with each other.



Scheme 1. a) Schematic representation of the PDMS thimbles used in this work, which were shaped as cylinders with a PDMS bottom and an open top. b) and c) The metathesis reaction occurs on the interior of the thimble, and the oxidation occurs on the exterior of the thimble. Here, G2 is Grubbs second-generation catalyst.

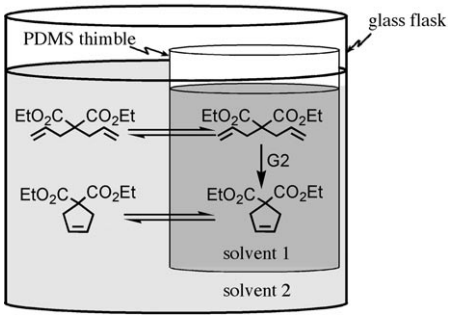
This work builds on and greatly expands our prior work on site-isolation of Grubbs catalysts by occlusion inside of PDMS slabs.[63,64] In this prior work, the Grubbs catalysts were swollen into a solid PDMS slab such that PDMS was the new solvent for the catalyst. Occlusion was very successful for site-isolation of the Grubbs catalyst, but limits remained as to the choice of solvents that could be used and some reagents reacted by olefin isomerization rather than metathesis. Occlusion was therefore useful for a set of reagents, but not a wider solution to site-isolation.

Encapsulation in a PDMS thimble allows the catalyst to remain dissolved in an organic solvent, is amenable to reactions with polar or apolar substrates, and is a general method for site-isolation of catalysts and reagents. It is critically important to note that we do not change the structures of the Grubbs catalyst or the MCPBA. We site-isolated the Grubbs catalyst by encapsulation even while it was freely dissolved in a solvent at reasonable concentrations.

In this paper we describe our method to fabricate PDMS thimbles and show how they can be used for site-isolation of the Grubbs catalysts from MCPBA. This site-isolation method allows cascade reactions that are not possible without PDMS thimbles. The immediate impact of this paper is that cascade reactions using metathesis catalysts and MCPBA will be possible for the first time. The long-term impact is a simple method to integrate organometallic catalysts with reagents that poison one another into cascade reactions without having to affect the structures either of the catalyst or of the reagent. This method should allow for a wide variety of catalysts and reagents to be integrated into cascade reactions without introduction of extra synthetic steps.

Results and Discussion

Determining the optimum solvent for encapsulating Grubbs catalysts in PDMS thimbles: A set of conditions was desired for site-isolation of the Grubbs catalysts in the interior of a PDMS thimble while allowing small molecules to diffuse from the exterior to the interior to react (Scheme 2). Specifically, a method was desired for adding reagents to the exterior of a PDMS thimble, having them diffuse into the thimble where the Grubbs catalyst was dissolved, reacting with the Grubbs catalyst, and diffusing out of the thimble while the Grubbs catalyst remained encapsulated. It would be necessary to keep the Grubbs catalysts site-isolated in the interior of the thimbles (rather than allow them to diffuse



Scheme 2. Reaction scheme for selective reagent transport and site-isolation of Grubbs catalyst from MCPBA. Diethyl diallylmalonate was added to the exterior of the PDMS thimble and diffused into the interior to react with the Grubbs catalyst. The product was then free to diffuse into the exterior.

through the PDMS) because this would allow a second reaction to take place outside the thimble without concern for whether reagents in the exterior would be poisoned by the Grubbs catalyst.

Although there exists a vast amount of literature on the rates of diffusion and the fluxes through PDMS for a variety of organic molecules, these data are incomplete for many of the molecules of interest for our work and are not directly applicable if PDMS is swelled by an organic solvent. Prior literature thus provides a useful guide for our work, but it is not possible to predict the correct solvent without measuring the flux for numerous molecules of interest under different solvent conditions. The literature was therefore used as a guide to select solvents and to test them for the ring-closing metathesis of diethyl diallylmalonate (Scheme 2).

Methylene chloride and 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6] (a room-temperature ionic liquid) were used as solvents for this reaction. Methylene chloride is a common solvent for Grubbs metathesis catalysts and swells PDMS well. [BMIM][PF_6] is a relatively new solvent that has been shown to be useful for metathesis reactions and is the opposite of methylene chloride in that it does not swell or diffuse into PDMS.[65–69] This result is not surprising and can be understood on the basis of the incompatibility of the hydrophobic matrix of PDMS and the ionic character of [BMIM][PF_6]. Through the choice of these two sets of solvents, it was possible to test the effect of swelling PDMS on the rates of reaction and whether it affected the encapsulation of Grubbs catalysts.

Table 1 shows the results for the reaction sequence shown in Scheme 2 in the presence of Grubbs first-generation catalyst and different solvents. Because [BMIM][PF_6] does not swell PDMS, we first studied whether the diethyl diallylmalonate could diffuse into the interior of the thimble at a reasonable rate. From Entries 1 and 2 in Table 1 it is clear that, although the rate of diffusion is enhanced by heating, the levels of conversion were low. An additional problem with this solvent was the poor solubility of the Grubbs catalyst.

[BMIM][PF_6] required a small amount of methylene chloride to be present to dissolve the catalyst fully. When methylene chloride was used, however, the catalyst rapidly diffused from the interior as seen visually. Grubbs catalyst forms a red solution when dissolved in methylene chloride; after reaction with a substrate resulting in the formation of a methylidene, this becomes an orange solution. Because of these colors, it was obvious by eye whether the catalyst was leaching from the interior of the PDMS thimble. Different solvent mixtures of methylene chloride and [BMIM][PF_6] were tested, and it was found that a 1:1 (v/v) mixture worked best.

Table 1. The effect of different solvents and temperatures on the ring-closing metathesis of diethyl diallylmalonate as shown in Scheme 2.

Entry[a]	Solvent[b]	t [h]	T [°C]	Conversion [%][c]	Leaching[d]
1	[BMIM]	72	25	5	no
2	[BMIM]	72	60	62	no
3	CH_2Cl_2	NA	25	NA[e]	yes
4	5:1 CH_2Cl_2/[BMIM]	3	25	100	yes
5	3:1 CH_2Cl_2/[BMIM]	5	25	100	yes
6	1:1 CH_2Cl_2/[BMIM]	9	25	72	no
7	1:1 CH_2Cl_2/[BMIM]	13	40	100	no
8[f]	1:1 CH_2Cl_2/[BMIM]	1	45	100	no

[a] Solvent in the interior (1.5 mL) together with 4 mol% of Grubbs first-generation catalyst were added to the interior of the thimble, whereas the same solvent (4.0 mL) was added to the exterior. [b] [BMIM] is the abbreviation for [BMIM][PF_6]. The ratios are based on volumes. [c] Conversion of the diethyl diallylmalonate to the cyclized product as determined by ^{1}H NMR spectroscopy. [d] Evidence for leaching of Grubbs catalyst from the interior of the thimble was monitored by eye through the color change of the solvent outside the thimble. [e] Conversion was not measured. [f] Grubbs second-generation catalyst was used.

To determine whether the Grubbs catalyst was remaining encapsulated, ring-closing experiments were carried out as shown in Scheme 2 with a 1:1 (v/v) solvent mixture of CH_2Cl_2/[BMIM][PF_6] both in the interior of the thimble and outside. Every four hours an aliquot was removed from the exterior and analyzed to determine the concentration of Ru by inductively coupled plasma-mass spectrometry (ICP-MS). The results in Table 2 show that the Grubbs catalyst remained mostly encapsulated, but it did leach to a small degree. To minimize the amount of catalyst that leached, we used a 1:1 (v/v) solvent mixture of MeOH/H_2O outside the thimble and repeated these experiments. This solvent mixture was chosen because the Grubbs catalyst is insoluble in it. The results in Table 2 clearly demonstrate that over 99.5% of the catalyst remained encapsulated in the interior of the thimble even after 16 h.

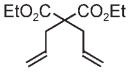
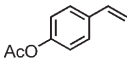
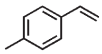
Table 2. Amount of Ru measured outside the PDMS thimbles as a function of time.

	CH_2Cl_2/[BMIM][PF_6] outside				MeOH/H_2O outside			
t [h]	[Ru] [mg mL^{-1}][a]	$[G2]_{outside}$ [mg mL^{-1}]	$\frac{[G2]_{interior}}{[G2]_{outside}}$[b]	Total G2 outside [%][c]	[Ru] [mg mL^{-1}][a]	$[G2]_{outside}$ [mg mL^{-1}]	$\frac{[G2]_{interior}}{[G2]_{outside}}$[b]	Total G2 outside [%][c]
4	0.066	0.55	76	4.6	0.0040	0.034	1300	0.28
8	0.144	1.21	35	10.0	0.0069	0.058	740	0.41[d]
12	0.154	1.30	32	10.7	0.0073	0.061	700	0.36[d]
16	0.196	1.65	26	13.6	0.0092	0.077	560	0.36

[a] Measured by ICP-MS of an aliquot (0.5 mL) taken from outside the PDMS thimble. [b] Ratio of the concentration of the Grubbs catalyst in the interior of the thimble to that outside. [c] The percentage of the amount of catalyst added to the reaction that leached from the interior of the thimble to the outside. [d] The percentage of G2 on the outside was lowered in the measurements made at 8 to 12 h because of the removal of 0.5 mL of solvent from outside the thimble to measure the concentration of Ru.

Metathesis with CH_2Cl_2/[BMIM][PF_6] 1:1 (v/v) in the interior and MeOH/H_2O 1:1 (v/v) outside: The results in the previous section demonstrated that the Grubbs catalyst would remain encapsulated if MeOH/H_2O was used as the solvent outside the thimbles. We allowed several reagents to react in the presence of encapsulated Grubbs catalysts to learn if this choice of solvents was compatible with our method. The results in Table 3 show that these reactions were complete in reasonable times with good yields.

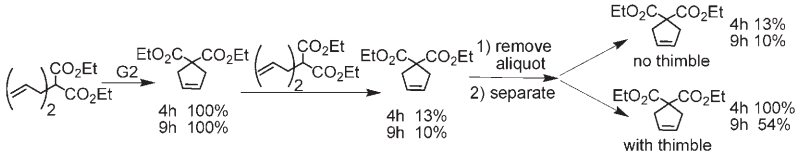
Table 3. Metathesis reactions in the presence of encapsulated catalyst dissolved in CH_2Cl_2/[BMIM][PF_6] (1:1 v/v) and a solvent mixture of MeOH/H_2O (1:1 v/v) outside the thimble.

Entry	Substrate	Catalyst[a]	t [h]	Yield [%][b]
1		G2	2.5	93
2		G2	2.5	87
3		G2	19	84
4		G2	26	69
5		G2	12	72

[a] These reactions were run at 4 mol% Grubbs second-generation catalyst at 45 °C. [b] Isolated yield after the reaction was complete.

Importantly, no color change of the MeOH/H_2O outside the thimble was observed even for the longest reaction times. In addition, the ICP-MS experiments described in Table 2 demonstrated that less than 0.5% of the Ru had leached into the exterior of the thimble after 16 h, but whether it was active metathesis catalyst or not still had to be determined. To answer this question, diethyl diallylmalonate was allowed to react in the presence of Grubbs second-generation catalyst and CH_2Cl_2/[BMIM][PF_6] as the solvent in the interiors of the thimbles and MeOH/H_2O as the solvent outside (Scheme 3). Diethyl diallylmalonate was added to the solvent outside the thimble and diffused through the PDMS walls to react. After 4 and 9 h, the levels of conversion outside the PDMS thimbles were determined to be 100%, and we then added another batch of diethyl diallylmalonate. The level of conversion outside the thimbles was immediately measured after the addition of diethyl diallylmalonate, and was found to be approximately 10% and 13% for the two times. The low levels of conversion reflect the fact that the diethyl diallylmalonate was added to the thimble exteriors whereas the product preferentially partitioned in the CH_2Cl_2/[BMIM]-[PF_6] found on the interiors of the thimbles. Subsequently, 2 mL of solvent from outside the thimbles was immediately removed and placed in a Schlenk flask under N_2. After 17 h, levels of conversion for the reactions carried out in the presence and in the absence of the PDMS thimbles were measured. The results indicated that little or no active metathesis catalyst was present in the solvent outside the thimbles after both 4 and 9 h. Thus, although less than 0.5% of the Ru had leached from the interiors of the thimbles, no active catalyst was found on the exterior. All of the metathesis reactions took place within the thimble, even though the reagents had been added to the exterior.

Cascade reactions with Grubbs catalyst and MCPBA: Our motivation in carrying out this research was to find a method for site-isolation of the Grubbs catalyst such that it could be used in cascade reactions with a poisonous second reagent. To demonstrate this method, we chose to allow substrates to undergo metathesis on the interiors of PDMS thimbles and epoxidation with MCPBA outside the thimbles. These two reactions were chosen because the importance of metathesis reactions and epoxidations in organic



Scheme 3. Reaction scheme used in the two control experiments to investigate leaching of Grubbs catalyst. No active Grubbs catalyst leached from the interiors of the thimbles to the outside.

chemistry would make their combination in cascade reactions a useful discovery.[70–77] In addition, evidence in the literature suggested that the Grubbs catalyst and MCPBA were incompatible.[78–86] In related work by others, it was shown that ruthenium compounds readily react with MCPBA to generate ruthenium oxo species.[79–82,85–87] These species oxidize alkenes and alkanes even at low loadings of Ru. This work made it reasonable to ask if the Grubbs catalyst was stable in the presence of MCPBA and whether it would catalytically poison MCPBA.

Control experiments were performed to demonstrate that the Grubbs catalyst poisons MCPBA. These control experiments were necessary to show that they must be site-isolated from each other—such as through the use of PDMS thimbles—and that the Grubbs catalyst catalytically decomposes MCPBA. In these control experiments, diethyl diallylmalonate was treated with Grubbs second-generation catalyst (4 to 0.1 mol%) to yield the cyclized product, and then MCPBA was added (Table 4). PDMS thimbles were not used, so the Grubbs catalyst was exposed to MCPBA. The metathesis reaction was first performed in CH_2Cl_2 (1 mL), and then MeOH with MCPBA (8 mL) was added. The levels of conversion were poor even for the lowest catalyst loadings. Entry 4 is notable because there were 3000 equivalents of MCPBA for every equivalent of Grubbs catalyst, yet the catalyst decomposed most of the MCPBA, resulting in only 22% conversion into epoxide. Additional reactions in which the cyclization was completed in a CH_2Cl_2/[BMIM]-[PF_6] mixture (1:1 v/v), followed by the addition of MCPBA dissolved in either MeOH or MeOH/H_2O, were attempted. Again, a vigorous reaction between MCPBA and the Grubbs catalyst was observed, and the epoxide was not seen by ^{1}H NMR spectroscopy. These reactions were important because they demonstrate the incompatibility of even catalytic amounts of Grubbs catalyst with MCPBA.

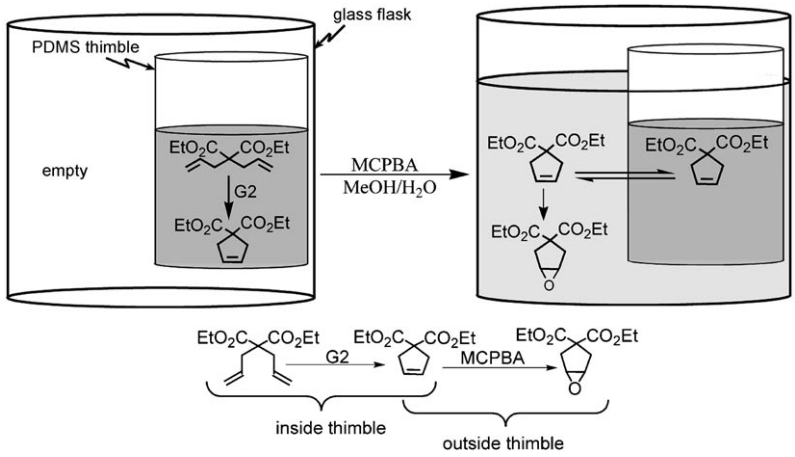
To carry out the cascade reaction, a two-step sequence was used to minimize leaching of the Grubbs catalyst from the PDMS thimble (Scheme 4). In these reactions, diethyl diallylmalonate was added to the interior of a thimble containing CH_2Cl_2/[BMIM][PF_6] (1:1 v/v, 1 mL) and the Grubbs catalyst. After the metathesis reaction was complete, MCPBA in MeOH/H_2O (8 mL) was added to the thimble exterior, and the epoxidation was allowed to go to completion. This sequence was successful, and the results for eight cascade reactions are shown in Table 5.

Recycling of the Grubbs catalyst within a cascade sequence: A key aspect to any claim of site-isolation is that the catalyst can be recycled. Our system allows for ease of recycling of a catalyst merely by removing the exterior solvent after the reaction is complete. To demonstrate this, Grubbs second-generation catalyst, CH_2Cl_2 (1 mL), and diethyl diallylmalonate were placed in the interior of a PDMS thimble. After one hour for the metathesis reaction, MeOH (20 mL) was added to the thimble exterior and was then removed after two hours. This procedure was repeated with the addition of more diethyl diallylmalonate to the thimble interior, followed again by MeOH (20 mL) to the thimble exterior. Scheme 5a shows that the levels of conversion were quantitative and that the yields were high over five recycling steps. The amount of ruthenium present in the thimble exterior for each cycle was measured by ICP-MS. It was found that over 97% of the catalyst remained encapsulated within the

Table 4. Control experiments to demonstrate that MCPBA is incompatible with Grubbs catalyst.

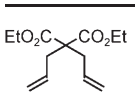
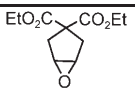
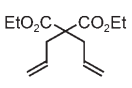
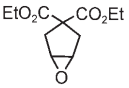
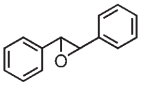
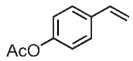
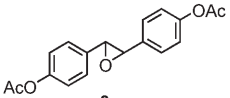
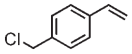
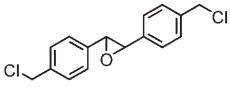
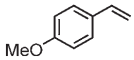
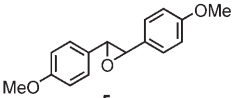
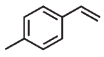
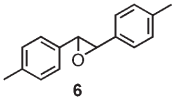
Entry	Solvent 1[a]	Solvent 2	G2 [equiv][b]	MCPBA [equiv][b]	MCPBA/G2	Epoxide [%][c]
1	CH_2Cl_2 (1 mL)	MeOH (8 mL)	0.04	3	75:1	<5
2	same as above		0.01	3	300:1	<5
3	same as above		0.004	3	750:1	8
4	same as above		0.001	3	3000:1	22
5	CH_2Cl_2/BMIM 1:1	MeOH	0.04	3	75:1	<5
6	CH_2Cl_2/BMIM 1:1	MeOH/H_2O 1:1	0.04	3	75/1	<5

[a] In each of these reactions the diethyl diallylmalonate (approximately 300 mg) and the indicated mol percent of Grubbs catalyst were added to solvent 1 and the system was allowed to react for 4 h. Next, solvent 2 was added together with the indicated equivalents (based on moles of diethyl diallylmalonate) of MCPBA, and the system was allowed to react for 7 h. [b] Equivalents based on diethyl diallylmalonate. [c] The level of conversion of the epoxide was determined by ^{1}H NMR spectroscopy; the remaining cyclic olefin had not reacted.



Scheme 4. The two-step, one-pot method used to carry out a cascade sequence. Firstly, diethyl diallylmalonate was allowed to react with encapsulated Grubbs catalyst in CH_2Cl_2/[BMIM][PF_6] (1:1). We next added MCPBA dissolved in MeOH/H_2O (1:1) to the thimble exterior.

Table 5. Cascade reactions with a variety of reagents as shown in Scheme 4.

Substrate	Product	$t_{metathesis}$ [h][a]	$t_{epoxidation}$ [h][a]	Mol% G2 (MCPBA [equiv])[b]	Yield [%][c]
	 **1**	4	12	4 (3)	71
		4	12	4 (10)	83
	 **2**	6	14	4 (5)	83
	 **3**	6	9	4 (5)	67
	 **4**	5	11	4 (5)	68
	 **5**	6	9	4 (5)	72
	 **6**	5	15	4 (5)	69

[a] These times refer to how long the metathesis and epoxidations reactions were allowed to run. [b] The mol% of Grubbs catalyst is shown, and the equivalents of MCPBA based on the moles of diethyl diallylmalonate are shown in parentheses. [c] Isolated yields.

thimble. To demonstrate the importance of this method further, the Grubbs catalyst was recycled even as it was integrated into a cascade sequence with MCPBA (Scheme 5b). It is particularly noteworthy that high yields were obtained for these reactions even after several recycling steps. The Grubbs catalyst can thus be recycled simply by removing the thimble from the reaction mixture, and this method is compatible with cascade reactions.

Conclusion

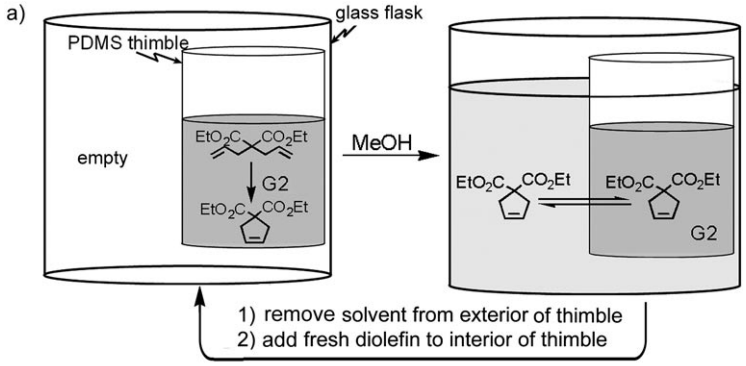
A simple, new method for site-isolation of Grubbs second-generation catalyst and MCPBA from each other is described; it allows them to be integrated into cascade reactions. Our method relies on the solid-state properties of PDMS thimbles for site-isolation of the large Grubbs catalyst from the polar MCPBA. These thimbles have high fluxes for small molecules, but ionic and large molecules have much lower fluxes; this allows them to be site-isolated within the PDMS thimbles. They remain either in the PDMS thimble interior or in the thimble exterior, while small molecules freely react on both sides.

The significance of this research is the demonstration of a new and simple method for site-isolation of homogeneous organometallic catalysts for use in cascade reactions and in reactions requiring that the catalyst be recycled. Although many useful homogeneous organometallic and inorganic catalysts that carry out one reaction in high yields have been developed over the preceding decades, they remain poorly integrated into cascade reactions because they are often poisoned by each other or by other reagents. To add these catalysts to cascade reactions successfully, they must be site-isolated from each other. Our method is a major advance in this field because we have site-isolated Grubbs catalyst without requiring a change in its ligand structure or attachment to a solid support. Furthermore, site-isolation was accomplished simply by addition to a PDMS thimble. These criteria are critical because they strongly suggest that our method may be applicable to other catalysts. We envision adding multiple catalysts or reagents straight from the manufacturer to different PDMS thimbles and carrying out cascade reactions that are not possible at the current time. In future work, we will explore these opportunities to increase the scope of our method such that a wider variety of cascade reactions can be envisioned.

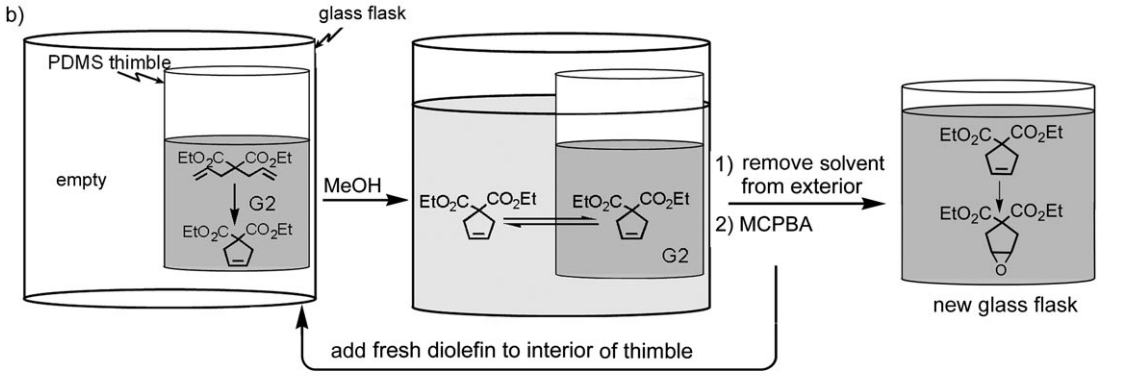
Experimental Section

Materials: Grubbs first- and second-generation catalysts were purchased from Aldrich, stored in a glovebox under nitrogen, and used as supplied. Substrates and reagents were purchased from Acros/Fisher (diallylamine, 4-acetoxystyrene, 4-methoxystyrene, styrene, 4-vinylbenzyl chloride, MCPBA, 1-chlorobutane, *N*-methylimidazole) or from Aldrich (diethyl diallylmalonate, hepta-1,6-dien-4-ol) and used as supplied. Organic solvents (except for the ionic liquid) were purchased from Acros or Aldrich at the highest purity and used as supplied. [BMIM][PF_6] was prepared by literature procedures.[65–69] All solvents used for metathesis reactions were degassed and maintained under nitrogen. The polydimethylsiloxane (PDMS) preparation kit (Sylgard 184) was purchased from Essex Brownell and used as supplied. Casting molds were made of brass. All reactions were performed under a nitrogen atmosphere with use either of Schlenk flasks or of a glove box unless otherwise stated.

Characterization: ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 instrument with $CDCl_3$ as solvent and TMS as an internal standard. Leaching of ruthenium from the thimbles was determined by ICP-MS on a Varian Ultra mass 700 ICP-MS with sensitivity of 0.001 mg mL^{-1} at the University of Iowa hygiene laboratories.



cycle	conversion / %	isolated yield / %
1	>98	66
2	>98	79
3	>98	75
4	>98	77
5	>98	82
6	70	na



cycle	conversion / %	isolated yield / %
1	>98	60
2	>98	80
3	>98	86
4	>98	81
5	>98	75

Scheme 5. a) Diethyl diallylmalonate was added to the interior of a PDMS thimble, it was allowed to react for 1 h, MeOH (20 mL) was added to the thimble exterior, cyclized product diffused to the thimble exterior, and the solvent was removed from the thimble exterior. The Grubbs catalyst was successfully recycled five times. b) A similar procedure was followed in a recycling/cascade sequence in which MCPBA was added to the solvent taken from the thimble exterior.

Preparation of PDMS thimbles: The two components from the PDMS kit were mixed in a ratio of 1:10 (*w*/*w*). The mixture was then degassed, placed in an oven maintained at 65 °C for ca. 5 min, and coated onto the brass rods. The PDMS was cured at 65 °C for 2 h, and the procedure was repeated once to yield tubes with thicknesses of 105 ± 22 μm. Once cured, the tubes were cut, and bottoms were added by placing thin films of degassed, partially pre-cured PDMS onto Petri dishes and allowing the tubes to stand in the PDMS while they fully cured. The finished thimbles were then cut to the desired height, soaked in hexanes followed by methylene chloride, and dried before use. The thicknesses of the thimbles were measured with a calibrated Fisher Micromaster optical microscope interfaced to a computer fitted with Micron1 imaging software.

General procedure for olefin metathesis reactions—diethyl cyclopent-3-ene-1,1-dicarboxylate: In a glove-box, Grubbs second-generation catalyst (43 mg, 0.05 mmol) was placed in a PDMS thimble contained in a Schlenk flask. The flask was sealed, removed from the glove box, and placed under N_2. Solvent mixtures (CH_2Cl_2/BMIM (1:1 v/v, 1 mL) and MeOH/H_2O (1:1 v/v, 4 mL) were added to the interior and exterior of the thimble. Next, diethyl diallylmalonate (300 μL, 1.25 mmol) was added to the thimble exterior, and the flask was placed in an oil bath maintained at 45 °C for 2.5 h. The reaction was cooled to room temperature, and the product was extracted with hexanes (3×10 mL). The hexane extracts were dried over anhydrous $MgSO_4$, solvent was removed in vacuo, and the product was purified by passage through a silica gel column with elution with EtOAc in hexanes (5%) to give the title compound as a light yellow liquid (0.25 mg, 1.16 mmol, 93% yield). The products from Table 3 had literature precedents; their characterization can be found in the Supporting Information.

Procedure for cascade reactions—diethyl 6-oxa-bicyclo[3:1.0]hexane-3,3-dicarboxylate (1): In a glove box, Grubbs second-generation catalyst (43 mg, 0.05 mmol) was placed in a PDMS thimble contained in a Schlenk flask. The flask was sealed, removed from the glove box, and placed under N_2. Solvent (1 mL of CH_2Cl_2/[BMIM][PF_6]) was added to the interior of the thimble, followed by diethyl diallylmalonate (300 μL, 1.25 mmol). The reaction mixture was allowed to stir at ambient conditions for 3 h, after which the flask was slowly charged with MCPBA (1 g, 3.7 mmol in MeOH/water 1:1 v/v, 8 mL) on the thimble exterior, and stirring was continued for a further 12 h. Solvent on the thimble exterior was removed, washed repeatedly with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3×10 mL). The thimble contents were extracted with hexanes (10 mL). The hexane and DCM extracts were pooled, washed with brine, and dried over anhydrous $MgSO_4$. Solvent was then removed in vacuo, and the product was purified on a silica gel column with elution with EtOAc (10%) to give the target epoxide in 71% yield (0.203 g, 0.89 mmol). The full characterization of molecules **1**–**6** is given in the Supporting Information.

Control experiments to demonstrate that the metathesis reaction was occurring in the interiors of the PDMS thimbles (Scheme 3): In a glove

box, Grubbs second-generation catalyst (43 mg, 0.05 mmol) was placed in a PDMS thimble contained in a Schlenk flask. The flask was sealed and removed from the glove box. With maintenance under nitrogen with the aid of a Schlenk line, DCM/[BMIM][PF_6] (1:1, 1 mL) was added to the interior of the thimble, while MeOH/H_2O (1:1, 4 mL) was added to the flask on the thimble exterior. Next, diethyl diallylmalonate (300 μL, 1.25 mmoles) was added to the exterior of the thimble and the flask was placed in an oil bath maintained at 45 °C for 4 h. An aliquot was removed and extracted with hexanes, and the hexanes extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The sample was analyzed by ^{1}H NMR spectroscopy to determine the level of conversion. Fresh diethyl diallylmalonate (300 μL, 1.25 mmol) was added to the thimble exterior and mixed thoroughly for ca. 2 min, after which an aliquot was removed and analyzed by NMR spectroscopy as detailed above. Next, half of the remaining solvent from the thimble exterior was transferred by syringe under N_2 to a Schlenk flask. Both flasks were heated at 45 °C for 14 h, after which they were analyzed for conversion by ^{1}H NMR spectroscopy.

Control experiments to demonstrate that Grubbs metathesis catalyst poisons MCPBA: In a glove box, a stock solution of Grubbs second-generation catalyst was prepared (39 mg in 10 mL CH_2Cl_2). An aliquot of the stock solution (280 μL, 1.09 mg, 0.013 mmol) was added to a Schlenk flask and further diluted with CH_2Cl_2 (720 μL). The flask was sealed, removed from the glove box, and attached to a Schlenk line. Diethyl diallylmalonate (300 μL, 1.25 mmol) was added, and the reaction was maintained at room temperature for 4 h. The flask was then charged with MeOH (8 mL) and MCPBA (0.92 g, 3.75 mmol). This reaction mixture was allowed to stir for 7 h, after which an aliquot was analyzed by ^{1}H NMR spectroscopy to determine the degree of conversion to the epoxide. This procedure was repeated similarly with different solvent mixtures and different ratios of Grubbs second-generation catalyst to MCPBA as summarized in Table 4.

Procedure for recycling encapsulated Grubbs second-generation catalysts (Scheme 5): In a glovebox, Grubbs second-generation catalyst (53 mg, 0.06 mmol) was placed in a PDMS thimble contained in a Schlenk flask. The flask was sealed, removed from the glove box, and placed under N_2. CH_2Cl_2 (1 mL) was added to the thimble, followed by diethyl diallylmalonate (300 μL, 1.25 mmol). This mixture was allowed to stir under N_2 at ambient temperature. After 1 h, MeOH (20 mL) was added to the thimble exterior. After 2 h, all the solvent on the exterior of thimble was removed, concentrated in vacuo, and weighed. Levels of conversion were determined by ^{1}H NMR spectroscopy. Fresh diethyl diallylmalonate (300 μL, 1.25 mmol) was added to the interior of the thimble. This procedure was repeated for a total of six cycles.

Procedure for recycling encapsulated Grubbs second-generation catalysts in a metathesis/epoxidation cascade sequence: The catalyst was recycled as described above, except that for each cycle the solvent in the thimble exterior was removed and placed in a new flask containing MCPBA (0.92 g, 3.74 mmol). The epoxidation reaction was allowed to run for 12 h. Conversion of the ring-closed olefin into the epoxide was confirmed to be >98% by ^{1}H NMR spectroscopy. The reaction mixture was then dissolved in CH_2Cl_2 (50 mL) and washed with water (100 mL), followed by saturated sodium bicarbonate (3×50 mL). The organic extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography with EtOAC in hexanes (10%) as the eluent. This procedure was repeated for a total of five cycles.

Acknowledgements

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