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Cascade Reactions

Cascade Reactions Using $LiAlH_4$ and Grignard Reagents in the Presence of Water**

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The development of cascade reactions—often called domino, tandem, or multicomponent reactions—is a major challenge in chemistry because of the difficulties in carrying out multiple reactions in one vessel.[1–4] These reactions are attractive goals because they save time and materials while producing less waste than the tradition method of carrying out reactions one at a time followed by purification and characterization of each product. In cascade reactions, two or more reactions are carried out in one reaction vessel so the number of purification and characterization steps are lowered which speeds up the synthesis. These reactions have the potential to change how molecules are synthesized in academic and industrial laboratories. For example, the synthesis of one kilogram of a pharmaceutical product typically yields 25 to 100 kilograms of waste; this amount of waste could be lowered through the use of cascade reactions.[3,5] Most methods to carry out cascade reactions use one catalyst that is responsible for catalyzing two or more reactions. Although highly successful when discovered, these reactions fail to use many of the catalysts and reagents that have been reported that are successful for one reaction but are not readily integrated into cascade sequences. An important frontier in this field is to develop methods to use multiple, commercially available catalysts or reagents in cascade reactions to increase the complexity of products that can be produced.

The key problem with cascade reactions that use multiple catalysts or reagents is that these components often poison each other. A solution to this problem is to site-isolate catalysts and reagents from each other such that they do not come into contact and poison one another. Site-isolation is typically carried out by bonding a catalyst to a polymer support, a heterogeneous surface, or encapsulating it within a sol–gel or zeolite.[2,4,6] For instance, in recent work Hawker, Fréchet, and co-workers attached acidic and basic residues to the interior of star polymers such that they did not quench each other, which allowed both acid- and base-catalyzed reactions in the same reaction vessel.[4] Site-isolation has challenges and limitations because it often requires additional synthetic steps and changes both the structure and activity of catalysts or reagents. In addition, the site-isolation of many reagents is challenging because all or part of their structures are integrated into the final product, thus affecting their structures to bond them to a support alters the final product. In addition, many reagents, such as water, $LiAlH_4$, and Grignard reagents, are commonly found in organic chemistry and are inexpensive, but they are not easily site-isolated. For instance, water and $LiAlH_4$ rapidly react with one another and can not be added to the same reaction vessel. Herein we will describe a general method to site-isolate water from $LiAlH_4$, Grignard, or cuprate reagents to carry out a series of cascade reactions using these reagents.

Our method for site-isolation of water from $LiAlH_4$ and Grignard reagents uses polydimethylsiloxane (PDMS) thimbles to completely encapsulate water (Figure 1). PDMS is a commercially available polymer that is very hydrophobic and has a low glass-transition temperature which leads to it being rubbery. PDMS is used as a membrane in separation devices because small molecules can diffuse through it readily; in fact, most small molecules have rates of diffusion and flux rates through PDMS that are within an order of magnitude of each other.[7] The flux rate is a measure of the moles of a molecule that pass through a slab of a material per unit time and describes whether the material allows large or small amounts of molecules to penetrate it on reasonable time scales. Although the flux rates of non-ionic organic molecules through PDMS are typically high, very polar molecules and water have low flux rates owing to their low solubilities in PDMS. In fact, other groups have shown that ionic molecules, such as ionic liquids, do not diffuse through PDMS because of their low solubility in the hydrophobic matrix of PDMS.[8] Water has a very low flux rate through PDMS owing to its

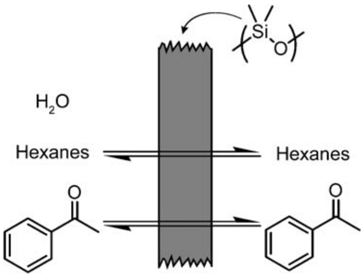

Figure 1. Hexanes and small, non-ionic organic molecules have high flux rates through PDMS (gray bar), but water has a low flux rate and has little tendency to cross the PDMS barrier.

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highly polar and hydrogen-bonding structure which is incompatible with the hydrophobic matrix of PDMS.

PDMS can be purchased as a two-component kit for approximately \$90 per kg and readily cast into a variety of shapes. The two components are mixed together to form a viscous liquid that cures into a solid after a few hours at 65 °C. We fabricated PDMS thimbles that were approximately 4 cm tall and 1.9 cm in diameter with walls that were 0.3 mm thick. These PDMS thimbles were made in approximately 1 h of work and allowed to cure overnight in an oven.

We expected that we could complete cascade reactions by encapsulating water and *p*-toluenesulfonic acid (*p*TsOH) to the interior of the thimbles and adding ionic reagents—such as $LiAlH_4$ and Grignard substrates—to the exterior of the thimbles. The idea is simple: small molecules will diffuse through PDMS and react on both sides of the thimbles, but water, $LiAlH_4$, Grignard, and cuprate reagents will not diffuse through PDMS and will remain site-isolated from each other.

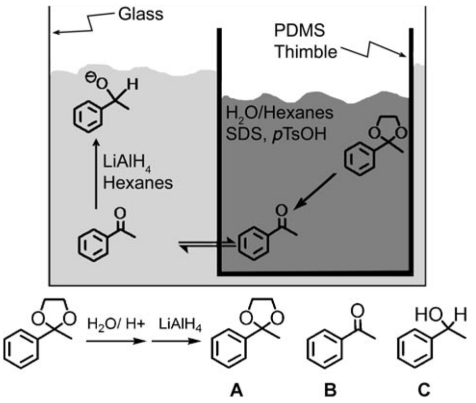


Figure 2. Initial method for cascade reactions: All of the solvents and reagents are added to the glass flask at the same time (see text and Table 1 for details).

Table 1: Solvent effect on the deprotection followed by reduction with $LiAlH_4$ in the presence of H_2O as shown in Figure 2.

Solvent	$LiAlH_4$ equiv	Conversion[a]		
		A	**B**	**C**
hexanes	0.25	0	55	45
hexanes	0.5	0	25	75
hexanes	0.75	0	10	90
hexanes	1.25	0	0	100 (89%)
CH_2Cl_2/hexanes[b]	1.25	0	3	97 (80%)
CH_2Cl_2	1.25	0	100	0
25% CH_2Cl_2:75% hexanes	1.25	0	20	80
50% CH_2Cl_2:50% hexanes	1.25	0	15	85
THF	1.25	0	60	40
25% THF:75% hexanes	1.25	5	15	80
50% THF:50% hexanes	1.25	0	50	50

[a] **A**, **B**, **C** are shown in Figure 2. The conversions were found by ^1H NMR spectroscopy of the crude reaction mixture. The yields of isolated selected products are shown in parentheses. [b] Methylene chloride was the solvent on the interior of the thimble and hexanes was the solvent on the exterior of the thimble.

We explored two different methods to illustrate this method by carrying out a cascade reaction where we first deprotected a cyclic ketal (2-methyl-2-phenyl-1,3-dioxolane) and then reduced the ketone to the alcohol with $LiAlH_4$. In our first method, we added all of the reagents, solvents, and thimble to the glass reaction vessel at the same time. In a typical reaction, we added 4 mL of water, 2 mL of an organic solvent, 0.2 g of sodium dococyl sulfate (SDS) as a detergent, and 0.5 g of the cyclic acetal to the inside of a PDMS thimble. To the outside of a PDMS thimble, we added 5 mL of an organic solvent and 0.145 g of $LiAlH_4$. The reaction was allowed to proceed for approximately 19 h. It is critical to note that we added over 50 equivalents of water to every molecule of $LiAlH_4$, only a thin wall of PDMS separated them. This barrier kept the water and $LiAlH_4$ from reacting to a significant extent, while allowing for rapid diffusion of the ketone (Figure 2, Table 1).

We first used hexanes as the organic solvent and studied the number of equivalents of $LiAlH_4$ that were needed to fully reduce the ketone. Our best success came from using 1.25 equivalents of $LiAlH_4$ for every equivalent of cyclic acetal. Although hexanes had an advantage because it swells PDMS and likely decreased the already slow diffusion of water through the PDMS by increasing the hydrophobicity of the membrane, many organic molecules have a poor solubility in it. To address this issue, we investigated other solvents. Methylene chloride and THF were poor choices because they swelled PDMS and allowed water to diffuse through and quench the $LiAlH_4$, so we sought to use them in combination with hexanes. Methylene chloride on the interior of the thimble and hexanes on the exterior of the thimble was a success and the yield of isolated product was 80%. Mixtures of methylene chloride or THF with hexanes gave incomplete conversions to the alcohol and suggested that diffusion of water to the exterior of the thimble was a problem with these solvent mixtures.

We explored a two-step/one-pot method to complete the same cascade sequence (Figure 3). In this method, we first added the solvents and reagents to the interior of the PDMS thimble and allowed the reaction to deprotect the cyclic acetal to proceed for approximately 5 h. Next, we added solvent and $LiAlH_4$ to the exterior of the thimble to reduce the ketone to the alcohol over 12 h. We took advantage of the much higher flux of the ketone relative to water to allow the ketone to diffuse out of the PDMS thimble and be reduced to the alcohol before enough water diffused from the thimble to influence the conversions. The results in Table 2 demonstrate that although methylene chloride and THF are not useful solvents by themselves, mixtures of each of these solvents with hexanes allows the reaction to go to completion. Thus, this reaction sequence is compatible with solvents that are commonly used in organic chemistry.

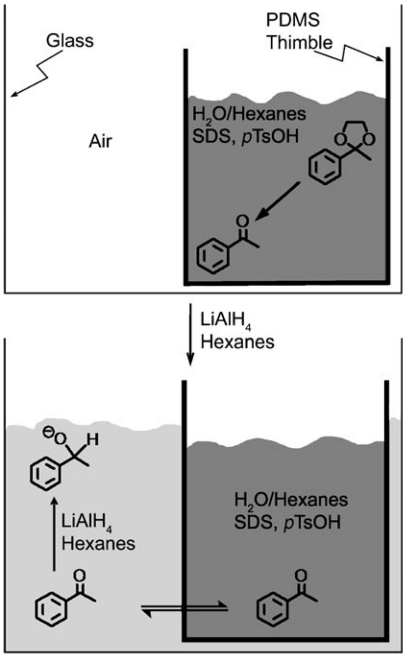


Figure 3. Improved method to carry out cascade reactions: First, the cyclic ketal is deprotected on the interior of the PDMS thimble. Next, $LiAlH_4$ and hexanes are added to the exterior of the thimble. The ketone diffuses rapidly across the PDMS barrier and reacts with the $LiAlH_4$, but water and *p*TsOH remain within the PDMS thimble.

Table 2: Different solvents for the conversion of the cyclic acetal into the alcohol using the two-step/one-pot sequence in Figure 3.

Solvent	Conversion[a]		
	A	**B**	**C**
25% CH_2Cl_2:75% hexanes	0	0	100 (86%)
50% CH_2Cl_2:50% hexanes	0	20	80
CH_2Cl_2	0	90	10
25% THF:75% hexanes	0	4	96
50% THF:50% hexanes	0	4	96 (76%)
75% THF:25% hexanes	0	40	60
THF	0	70	30

[a] **A**, **B**, **C** are shown in Figure 2. The conversions were found by ^1H NMR spectroscopy of the crude reaction mixture. The yields of selected isolated products are shown in parentheses.

We wished to study whether our method could site-isolate water from very reactive Grignard and alkyl lithium reagents (Figure 4). These reagents are clearly very incompatible with water, but because of the ionic bond in Grignard and alkyl lithium reagents we expected that their flux through PDMS would be very low in comparison to non-ionic molecules. Because of the success of the two-step/one-pot reaction sequence with $LiAlH_4$, we used this method for reactions with these nucleophiles. Typical conditions included 4 mL of water, 2 mL of hexanes, 0.5 g of the cyclic acetal, and 0.2 g of sodium docecyl sulfate on the interior of the thimble. After deprotection for 5 h, we added the 5 to 8 equivalents of the Grignard reagent or butyllithium and a solvent mixture of hexanes and diethyl ether to the exterior of the thimble and allowed it to react for 12 to 24 h. These reactions were very successful and gave high yields of the tertiary alcohol (Table 3) despite the presence of over 10 equivalents of water for every Grignard reagent in the reaction vessel. Thus, this method successfully site-isolated water from alkyl lithium and Grignard reagents.

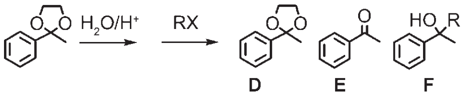
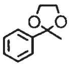
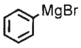
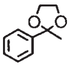
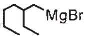
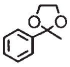
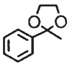
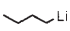
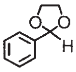
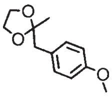


Figure 4. Deprotection of a cyclic ketal using water in a PDMS thimble followed by reaction with a nucleophile (RX) in the exterior of a PDMS thimble.

Table 3: Different cyclic ketals treated by deprotection then reaction with a variety of nucleophiles as shown in Figure 4.

Ketal[a]	Nucleophile[b]	*t* [h][c]	Conversion[d]		
			D	**E**	**F**
		5/16	5	0	95 (93%)
		4/12	0	2	98 (81%)
		5/14	0	2	98 (79%)
		5/11	0	10	90
	Bu_2CuLi	3.5/12	0	0	100 (87%)
	Bu_2CuLi	12/22	2	2	96 (77%)
	$LiAlH_4$	5/24	0	2	98 (84%)

[a] The solvent on the interior of the thimbles was hexanes but the solvent on the exterior of the thimbles varied. For the Grignard reagents it was a mixture of diethyl ether and hexanes, for butyllithium and $LiAlH_4$ it was hexanes, and for the cuprates it was a mixture of diethyl ether and hexanes. [b] Five to eight equivalents of nucleophile were added for every equivalent of cyclic acetal. [c] The first number shows the time we allowed the deprotection to run before the addition of solvent to the exterior of the thimble. The second number is the time the reaction with the nucleophile was allowed to run before the reaction mixture was quenched. [d] **D**, **E**, **F** are shown in Figure 4. The conversions were found by ^1H NMR spectroscopy of the crude reaction mixture. The yields of selected isolated products are shown in parentheses.

We observed that alkyl lithium and Grignard reagents reacted with PDMS which made adding them in excess necessary. In fact, butyllithium dissolved most of the PDMS membrane within 10 min. Although this reaction was able to reach 90% conversion, PDMS side products contaminated the reaction mixture. Grignard reagents were not as reactive towards the PDMS membrane as butyllithium, but their effect was noticeable. After the reaction was complete, the PDMS thimble was not as rubbery as before the Grignard reagent was introduced and a white solid accumulated on the exterior of the thimbles during reactions with Grignard reagents. As a result of the reactivity of alkyl lithium and Grignard reagents towards the PDMS thimbles, we decided to investigate a less reactive nucleophile: lithium dialkyl cuprates. We treated a dialkyl cuprate with an aldehyde and a ketone to demonstrate that this cascade sequence could yield secondary and tertiary alcohols.

Although our cascade reactions were successful, the reactivity of PDMS thimbles towards strong nucleophiles is a weakness. To address this issue, we fabricated new thimbles from a 1:1 by volume mixture of cyclooctene/dicyclopentadiene that was polymerized with the Grubbs' second-generation catalyst. We used a total monomer to catalyst ratio of 21000:1 which yielded a highly crosslinked polymer thimble that was structurally rigid and flexible. The full details for the fabrication can be found in the supporting information. These thimbles only have carbon–carbon single and double bonds and have higher stabilities towards strong nucleophiles than thimbles fabricated from PDMS. Furthermore, hydrogenation of the olefins would result in even less-reactive thimbles, but we have not explored this option yet.

To investigate whether these thimbles were stable towards strong nucleophiles, we initially exposed them to butyllithium and phenyl magnesium bromide with no apparent effect after several hours. In comparison, the PDMS thimbles reacted rapidly and noticeably with these reagents. Next, we carried out a two-step cascade sequence similar to those described in Figure 4 except that we used the new polycyclooctene/polydicyclopentadiene thimbles. We isolated an 81% yield of the desired product despite having over 41 equivalents of water for each molecule of butyllithium and adding only 2.0 equivalents of butyllithium for every equivalent of ketone.

To demonstrate that the polycyclooctene/polydicyclopentadiene thimbles were stable towards Grignard reagents, we treated phenyl magnesium bromide in the same reaction sequence shown in Figure 4 to yield the desired product in 95% yield. These results demonstrate that our new thimbles allowed for the selective diffusion of small organic molecules over water, and they provide another option to consider for these cascade reactions.

Many more cascade reactions are possible with this method, including those that use inorganic catalysts or reagents (Figure 5). For instance, we carried out a Wacker oxidation of *p*-methylstyrene by adding $PdCl_2$ and CuCl to the interior of a PDMS thimble along with DMF, H_2O, and an O_2 balloon. After the oxidation was complete, we added hexanes and $LiAlH_4$ to the outside of the thimble to yield the alcohol in 66% yield. This reaction sequence was noteworthy because we added an excess of water such that all of the $LiAlH_4$ would have been quenched if these reagents had not been separated by the PDMS thimble. Also, because Pd/Cu remained mostly encapsulated within the thimble they were site-isolated from the product such that it was straightforward to clean. This is important because Pd/Cu impurities must be removed to yield a clean product.

In another example, we fabricated an amide starting from an alcohol and amine in a one-pot cascade reaction (Figure 5). We added a catalytic amount of pyridinium chlorochromate (PCC) and H_5IO_6 to the interior of a PDMS thimble along with methylene chloride/DMF. 1-Octanol was added to this mixture, oxidized, and then allowed to diffuse from the thimble by the addition of methylene chloride/DMF to the outside of the thimble. Finally, benzyl amine was used to form the amide in 71% yield. Control reactions demonstrated that this reaction sequence was not successful without a PDMS thimble because PCC/H_5IO_6 rapidly reacted with DCC. This cascade reaction provides a simple method to form amide bonds starting from alcohols and amines by using PDMS thimbles.

In conclusion, we report a novel use of PDMS and polycyclooctene/polydicyclopentadiene thimbles to site-isolate incompatible reagents and catalysts to perform cascade reactions. PDMS is a cheap, relatively inert, commercially available material that can be easily cast into reaction vessels with different sizes and shapes. This material has many beneficial properties for cascade reactions including its high flux rate towards many non-ionic organic molecules that contrasts with its low flux rates for water and ionic molecules. This difference in flux rates allows incompatible reagents to remain on the interior or exterior of PDMS thimbles for a long time—they are site-isolated from each other. We believe that our method to carry out cascade reactions using thimbles will be a useful tool in the synthesis of organic molecules by cascade reactions because it allows multiple reagents and catalysts to be used without regard for whether they poison one another. The strength of this method is the ease with which ionic and polar reagents and catalysts can be site-isolated from each other while organic molecules can react with both sets.

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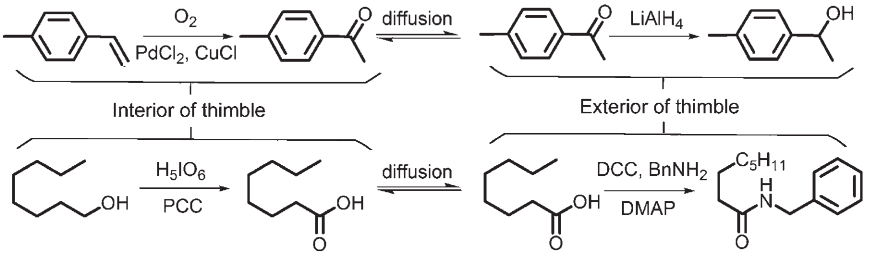

Figure 5. Two cascade reactions that were carried out using PDMS thimbles in glass flasks. DCC = N,N′dicyclohexyl methanediimine, DMAP = 4-dimethylaminopyridine.

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