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# Sequential Reactions with Grubbs Catalyst and AD-mix-α/β Using PDMS Thimbles

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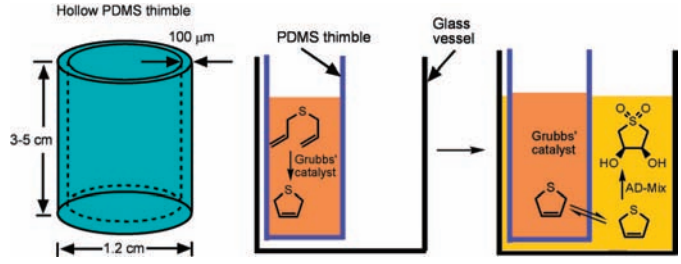
## ABSTRACT




**Incompatible Grubbs catalyst and an osmium dihydroxylation catalyst were site-isolated from each other using polydimethylsiloxane thimbles. The Grubbs catalyst was added to the interior of the thimbles, and AD-mix-α/β was added to the exterior. Organic substrates readily fluxed through the walls of the thimbles and reacted with each catalyst. A series of cascade reactions were developed including those with intermediates possessing low boiling points or that were foul smelling.**

Many excellent examples of homogeneous catalysts have been developed that catalyzed one reaction in high yields. The use of catalysts necessitates that reactions be carried out sequentially because catalysts often poison one another or require different solvents, temperatures, or reagents that make the addition of more than one catalyst to a reaction vessel problematic. This limitation makes it necessary to isolate and purify the product of each reaction before the next reaction can be carried out which increases the time, cost, and waste associated with a multistep synthesis.[1] A challenge in the field of catalysis is to develop methods to site-isolate catalysts from one another such that two or more catalysts can be added to a reaction vessel to catalyze more than one reaction. The desired method should be general and allow for a multitude of well-developed, commercially available catalysts to be site-isolated from each other with little to no modification of their ligand structures.

Many approaches to site-isolate catalysts have been developed that involve bonding catalysts to silica, zeolites, polymers, or other solid supports.[2] These methods require covalent modifications of the catalysts that add synthetic steps to a synthesis and result in new catalysts with activities that are often lower than the original versions. Methods that do not require modification of the catalysts, such as through incarceration in zeolites or polymer microspheres, either lead to leaching or use unknown mechanisms for site-isolation.[3]

(1) (a) Sheldon, R. A. *J. Chem. Tech. Biotechnol.* **1997**, *68*, 381–388. (b) Sheldon, R. A. *Chem. Commun.* **2008**, *29*, 3352–3365.

(2) (a) Stasiak, M.; Studer, A.; Greiner, A.; Wendorff, J. H. *Chem.—Eur. J.* **2007**, *13*, 6150–6156. (b) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2005**, *127*, 9674–9675. (c) Helms, B.; Guillaudeu, S. J.; Xie, Y.; McMurdo, M.; Hawker, C. J.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6384–6387. (d) Zheng, X.; Jones, C. W.; Weck, M. *Chem.—Eur. J.* **2006**, *12*, 576–583. (e) Breinbauer, R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 3604–3607. (f) Jezequel, M.; Dufaud, V.; Ruiz-Garcia, M. J.; Carrillo-Hermosilla, F.; Neugebauer, U.; Niccolai, G. P.; Lebfebvre, F.; Bayard, F.; Corker, J.; Fiddy, S.; Evans, J.; Broyer, J.-P.; Malinge, J.; Basset, J.-M. *J. Am. Chem. Soc.* **2001**, *123*, 3520–3540. (g) Yamada, Y. M. A.; Uozumi, Y. *Tetrahedron* **2007**, *63*, 8492–8498. (h) Kim, J.-W.; Kim, J.-H.; Lee, D.-H.; Lee, Y.-S. *Tetrahedron Lett.* **2006**, *47*, 4745–4748. (i) Dell'Anna, M. M.; Lofu, A.; Mastrorilli, P.; Mucciante, V.; Nobile, C. F. *J. Organomet. Chem.* **2006**, *691*, 131–137. (j) Helms, B.; Liang, C. O.; Hawker, C. J.; Frechet, J. M. J. *Macromolecules* **2005**, *38*, 5411–5415. (k) Drelinkiewicza, A.; Waksmundzka, A.; Makowski, W.; Sobczak, J. W.; Krol, A.; Zieba, A. *Catal. Lett.* **2004**, *94*, 143–156. (l) Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385–3465.

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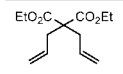
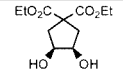
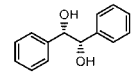
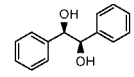
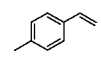
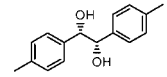
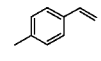
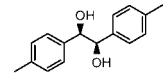
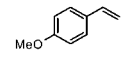
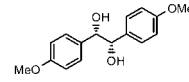
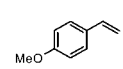
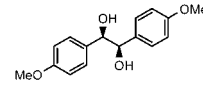
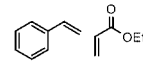
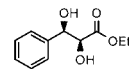
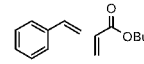
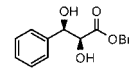
We recently reported a new approach to site-isolation of catalysts using polydimethylsiloxane (PDMS) thimbles that does not require modification of the catalysts for site isolation.[4,5] A catalyst is added to the interior of the PDMS thimble and allowed to react with reagents that flux through the walls of the thimble. The catalyst remains encapsulated in the interior of the thimble and is site-isolated from a second catalyst or reagent on the exterior of the thimble. In recent work, we site-isolated the Grubbs catalyst from a reagent, *m*-chloroperoxybenzoic acid (*m*-CPBA), that was poisoned at loadings as low as one Grubbs catalyst for every 3000 equiv of *m*-CPBA. The Grubbs catalyst was placed on the interior of the thimble, and over 99.5% of it remained on the interior even after 16 h. In contrast, organic substrates readily fluxed through the PDMS walls and reacted with *m*-CPBA that was found on the exterior of the thimbles. The reason for the low flux of the Grubbs catalyst was its size (large molecules, such as the Grubbs catalyst, have lower flux than small molecules) and insolubility in the solvent on the exterior of the thimbles.[4]

This work was extended in this publication to show how two critically important inorganic catalysts can be site-isolated from each other. Specifically, the Grubbs catalyst and the Sharpless dihydroxylation catalyst were chosen due to the importance of both catalysts in organic synthesis.[6] Each of these catalysts catalyzes their respective reactions to yields that often exceed 90% and, for the $OsO_4$ catalyst, in high enantioselectivities. Unfortunately, these catalysts poison one another such that they can not be added to the same reaction vessel, and they require different solvent systems. Furthermore, the fluxional ligand structure around $OsO_4$ precludes its attachment to a solid support, which makes its site-isolation from a second catalyst even more challenging.

The first step in these cascade reactions was the metathesis reaction catalyzed by the Grubbs second-generation catalyst within a PDMS thimble. PDMS thimbles were fabricated with widths of 1.2 cm, heights of 3−5 cm, and walls that were 100 $\mu$m thick. The fabrication was simple, and dozens were made in an afternoon.[4] The metathesis reactions were allowed to proceed to completion with reaction times from 2 to 8 h. In the second step, AD-mix was added to the exterior of the thimbles in either a 1/1 mixture of *t*-butyl alcohol/$H_2O$ or a 1/2/3 mixture of BMIM/$H_2O$/acetone. Here, BMIM is an abbreviation for a common ionic liquid: 1-butyl-3-methylimidazolium hexafluorophosphate. Both sets of solvent are commonly used with AD-mix and allow the reaction to proceed in high yields with high enantioselectivities.[7] Each solvent mixture formed two layers, but in neither system was the Grubbs catalyst soluble.

**Table 1.** Results of Cascade Reactions

| substrate | product | time[a] (h/h) | AD-mix | yield/ee[b] (%/%) |
|---|---|---|---|---|
|  |  | 2/36[c] | α | 68[d] |
| Same as above | Same as above | 2/36 | α | 75[d] |
|  |  | 4/36 | α | 82/63[e] |
|  |  | 6/13 | α | 72/85 |
|  |  | 9/16 | β | 72/98 |
|  |  | 8/12 | α | 86/84 |
|  |  | 8/16 | β | 95/98 |
|  |  | 6/12 | α | 61/93 |
|  |  | 7/22 | β | 87/98 |
|  |  | 10/13 | β | 82/98 |
|  |  | 8/20 | β | 78/98 |

[a] Time for metathesis/time for dihydroxylation. [b] Isolated yield/enantiomeric excess. [c] 1/1 (v/v) *t*-BuOH/$H_2O$ was used as the solvent for this reaction. 1/2/3 (v/v/v) BMIM/$H_2O$/acetone was used for all other reactions. [d] The product is achiral. [e] Diastereomeric excess.

The results in Table 1 demonstrate that this method was successful for ring-closing metathesis, homocross metathesis, and heterocross metathesis reactions. The yields and enantioselectivities were high for each reaction and comparable to what was observed for AD-mix-α/$\beta$ when used by others to carry out one-step reactions. This cascade sequence is very attractive for allowing simple, two-step cascade reactions to


(3) (a) Ogunwumi, S. B.; Bein, T. *Chem. Commun.* **1997**, *n/a*, 901–902. Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412–3413. (b) Sabater, M. J.; Corma, A.; Domenech, A.; Fornes, V.; Garcia, H. *Chem. Commun.* **1997**, *n/z*, 1285–1286. (c) Avnir, D.; Coradin, T.; Lev, O.; Livage, J. *J. Mater. Chem.* **2006**, *16*, 1013–1030. (d) Hagio, H.; Sugiura, M.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 375–378. (e) Miyamura, H.; Akiyama, R.; Ishida, T.; Matsubara, R.; Takeuchi, M.; Kobayashi, S. *Tetrahedron* **2005**, *61*, 12177–12185. (f) Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 2871–2873.

(4) (a) Mwangi, M. T.; Runge, M. B.; Hoak, K. M.; Schulz, M. D.; Bowden, N. B. *Chem.—Eur. J.* **2008**, *14*, 6780–6788. (b) Runge, M. B.; Mwangi, M. T.; Miller, A. L.; Perring, M.; Bowden, N. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 935–939.

(5) (a) Runge, M. B.; Mwangi, M. T.; Bowden, N. B. *J. Organomet. Chem.* **2006**, *691*, 5278–5288. (b) Mwangi, M. T.; Runge, M. B.; Bowden, N. B. *J. Am. Chem. Soc.* **2006**, *128*, 14434–14435.

(6) (a) Andersson, M. A.; Epple, R.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 472–475. (b) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278–1291. (c) Pelly, S. C.; Parkinson, C. J.; Van Otterlo, W. A. L.; De Koning, C. B. *J. Org. Chem.* **2005**, *70*, 10474–10481. (d) Formentin, P.; Gimeno, N.; Steinke, J. H. G.; Vilar, R. *J. Org. Chem.* **2005**, *70*, 8235–8238. (e) Zarka, M. T.; Nuyken, O.; Weberskirch, R. *Macromol. Rapid Commun.* **2004**, *25*, 858–862. (f) Grubbs, R. H. *Handbook of Metathesis Catalysts*; Wiley-VCH: Weinheim, 2003. (g) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (h) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554. (i) Neisius, N. M.; Plietker, B. *J. Org. Chem.* **2008**, *73*, 3218–3227.

(7) (a) Branco, L. C.; Afonso, C. A. M. *Chem. Commun.* **2002**, *24*, 3036–3037. (b) Branco, L. C.; Afonso, C. A. M. *J. Org. Chem.* **2004**, *69*, 4381–4389.

be carried out on intermediates with high boiling points and varying solubilities in organic solvents. These intermediates would be challenging to remove from residual Grubbs catalyst using liquid−liquid extractions or distillation such that other methods to site-isolate the Grubbs catalyst would likely fail. In contrast, the method reported here allows each catalyst to each react in their own solvents, at desired concentrations, and as homogeneous catalysts. The catalysts were site-isolated by thin polymeric walls.

These cascade reactions required the sequential addition of catalysts to complete the reaction sequence in high yields. In many cascade sequences, it is critically important *not* to add all catalysts and reagents to one reaction vessel at the same time because the order of reaction of the catalysts must be controlled. For instance, in our reactions, AD-mix can react with the starting materials prior to the metathesis reaction to yield a very different product than the desired one. It is absolutely necessary to control the order of reactions, and the method reported in this paper provides one method to solve this problem by the addition of AD-mix after the metathesis reaction is complete. The sequential addition of catalysts is an advantage in some instances over a simultaneous addition and allows for inline control of the reactions to reduce waste and improve efficiency. Importantly, our method provides a solution to control the order of reaction of catalysts without requiring any synthetic transformations to them or the reagents.

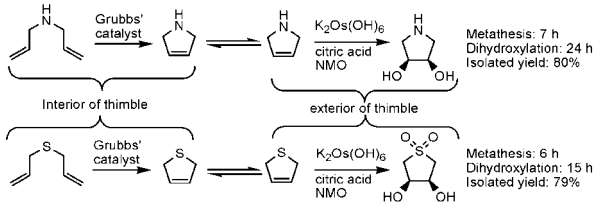



**Figure 1.** Cascade reactions with challenging intermediates. NMO is *N*-methylmorpholine.

It is important that this method can also be applied to reactions where the products of the first reaction in a cascade sequence have low boiling points or other physical properties that make them challenging to isolate and characterize. For instance, diallylamine (boiling point = 111−112 °C) is commonly used in metathesis reactions to demonstrate reactivities of new catalysts, but the product is rarely isolated because of its low boiling point which is estimated to be approximately 55 °C.[8] To address this problem, diallylamine was protonated to facilitate its reaction with the Grubbs catalyst on the interior of a PDMS thimble to yield 2,5-dihydropyrrole, which was deprotonated to allow for fast flux through the walls of the thimble. $K_2Os(OH)_6$ was added to the exterior of the thimble and reacted with 2,5-dihydropyrrole to yield *cis*-3,4-pyrrolidinediol in 80% yield (Figure 1). This product had an estimated boiling point of 167 °C and was simple to isolate.

Another synthetic challenge this cascade sequence solves is how to obviate the need to isolate potentially foul smelling products. Functionalized thiophenes are important materials in medicinal chemistry, but they are often synthesized in multiple steps to lessen the need to isolate low boiling point thiols or sulfides.[9] The synthesis of 1,1-dioxio-3,4-thiopheneoxide was undertaken to demonstrate the ability of our cascade sequence to complete a challenging set of reactions in one pot (Figure 1). First, diallyl sulfide was reacted with encapsulated Grubbs catalyst to yield a foul smelling intermediate with a boiling point of 90 °C. This product was not isolated; rather, $K_2Os(OH)_6$ was added to the exterior to dihydroxylate the olefin and oxidize the sulfur. The final product was a white solid that did not have a foul odor. This approach was an example of three reactions in one reaction vessel that eliminated the need to isolate a foul smelling intermediate.

**Table 2.** Flux of Os and Ru through PDMS

| solvent[a] | time[b] (h) | Os on interior (%) | Os on exterior (%) | Ru on interior (%) | Ru on exterior (%) |
|---|---|---|---|---|---|
| 1/2/3 | 10 | 1.1 | 98.9 | 99.78 | 0.22 |
| 1/2/3 | 25 | <dl | 100 | 99.40 | 0.60 |
| 1/1 | 10 | 10.3 | 89.7 | 99.65 | 0.35 |
| 1/1 | 24 | 79.4 | 20.6 | 99.09 | 0.91 |

[a] 1/2/3 refers to the v/v/v mixture of BMIM/$H_2O$/acetone, and 1/1 refers to the v/v mixture of *t*-BuOH/$H_2O$. Fifteen milliliters of the solvent was added to the exterior of the thimble. [b] Time for the dihydroxylation reaction.

To address how much Ru leached to the exterior of the thimble and how much Os leached to the interior, a set of control experiments with diethyl diallylmalonate were carried out and the concentrations of the metals were found using inductively coupled plasma mass spectroscopy (ICP-MS). The metathesis reaction was completed in 1 h in 1 mL of $CH_2Cl_2$/BMIM on the interior of a PDMS thimble followed by the addition of solvent and AD-mix to the exterior of the thimble. It is clear from the results in Table 2 that the Ru was site-isolated because less than 1% diffused to exterior of the thimble even after 25 h. This result is notable because the organic substrates in Table 1 and Figure 1 both fluxed to the exterior and were dihydroxylated in times that were typically less than 24 h. The flux of Os was similarly low when the 1/2/3 (BMIM/$H_2O$/acetone) solvent mixture was used for the dihydroxylation. In these reactions, the amount of Os that fluxed to the interior of the thimbles was approximately 1%. When the 1/1 (*t*-BuOH/$H_2O$) solvent mixture was used on the exterior of the thimbles, the amount of Os that fluxed to the interior was significantly higher.

(8) (a) Jafarpour, L.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5416–5419. (b) Binder, J. B.; Blank, J. J.; Raines, R. T. *Org. Lett.* **2007**, *9*, 4885–4888.

(9) (a) Hafez, H. N.; El-Gazzar, A. B. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5222–5227. (b) Molvi, K. I.; Vasu, K. K.; Yerande, S. G.; Sudarsanam, V.; Haque, N. *Eur. J. Med. Chem.* **2007**, *42*, 1049–1058. (c) Sperry, J. B.; Wright, D. L. *Curr. Opin. Drug Dis. Dev.* **2005**, *86*, 723–740.

These results suggest that the Os fluxed through the walls of the thimbles rather than through vapor phase to the interior of the thimbles and that the solvent conditions can be optimized to site-isolate Os and Ru.

To demonstrate the incompatibility of the Grubbs catalyst with AD-mix, a series of reactions were completed without PDMS thimbles to separate the catalysts. In these reactions, diethyl diallylmalonate was reacted with the Grubbs catalyst followed by the addition of additional solvent and AD-mix to complete the dihydroxylation (Table 3). The question was not whether AD-mix poisoned the Grubbs catalyst; rather it was whether the Grubbs catalyst poisoned AD-mix. At 4 mol % of the Grubbs catalyst, only the metathesis product was observed with no evidence of the dihydroxylation product, and at loadings of 1 mol % the reaction had a conversion of only 60% to the diol. Only when the loading of the Grubbs catalyst was at or below 0.1 mol % of the malonate did the cascade reaction succeed and the diol was obtained. This result is important because many metathesis reactions reported in the literature use 1 mol % or higher loadings of catalyst.

**Table 3.** Cascade Reactions with Diethyl Diallylmalonate in the Absence of Thimbles

| G2[a,b] (equiv) | AD-mix-α[b] (equiv of Os) | G2/Os/Fe | olefin[c] (%) | diol[c] (%) |
|---|---|---|---|---|
| 0.04 | 0.004 | 10/1/1350 | >98 | <2 |
| 0.01 | 0.004 | 2.5/1/1350 | 40 | 60 |
| 0.001 | 0.004 | 1/4/5400 | 5 | 95 |
| 0.01 | 1 | 1/10/0 | 95 | 5 |

[a] G2 refers to the Grubbs catalyst. [b] Equivalents are based on ratio of metal to diethyl diallylmalonate. [c] Ratio of cyclized product to the dihydroxylated product after 24 h.

These results demonstrated that the dihydroxylation reaction was poisoned by the Grubbs catalyst, but due to the complexity of AD-mix, it was not clear how the poisoning occurred. To investigate whether the Grubbs catalyst reacted with Os or ferricyanide that is found in AD-mix at a ratio of 1350 parts of ferricyanide for every part Os, the metathesis reaction was run to completion followed by the addition of 1 equiv of Os for every olefin in the cyclized product. No ferricyanide was added to this reaction sequence. This reaction yielded 95% of the cyclized olefin and only 5% of the diol and clearly demonstrated that the Grubbs catalyst deactivated the Os catalyst at low loadings. The exact nature of the deactivated species was not studied, but it was consistent with the rapid reaction between the Grubbs catalyst and strong oxidants such as *m*-chloroperoxybenzoic acid.[4]

Recycling of the Grubbs catalyst within the cascade sequence was possible because it was site-isolated within thimbles. In these reactions, diallyl diethylmalonate was added to the interior of PDMS thimbles in a 1/1 v/v mixture of $CH_2Cl_2$/BMIM and allowed to react for 1 h. Next, 15 mL of 1/1 *t*-BuOH/$H_2O$ was added to the exterior of the thimble and the cyclized metathesis product was allowed to diffuse to the exterior. After 1 h, the *t*-BuOH/$H_2O$ mixture was transferred to a different reaction vessel and AD-mix was added to it and a new batch of diethyl diallylmalonate was added to the interior of the PDMS thimble. This eluant was transferred to a new flask due to the finite lifetime of the Grubbs catalyst and the long reaction times required for AD-mix. The transfer of eluant was simple and rapid. This process was repeated seven times without loss of activity of the Grubbs catalyst, and the isolated yields of the product of the cascade sequence averaged 80%.

The method reported in this article offers a solution for how to complete multistep cascade reactions for catalysts that poison one another or require reaction conditions that are incompatible. Notably, the structures of the catalysts were not modified; they were used as received so additional synthetic steps to them were not necessary. Cascade reactions were demonstrated for sequences that had challenging intermediates, and, importantly, recycling was possible within a cascade sequence. We believe that this method will prove to be general and other catalysts can be site-isolated using this simple procedure.

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**Supporting Information Available:** Experimental procedures and compound characterization are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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