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Protection of Ruthenium Olefin Metathesis Catalysts by Encapsulation in a Self-assembled Resorcinarene Capsule

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Catalyst encapsulation is examined as a means of increasing the productivity of olefin metathesis catalysts. Commercially available, cationic ruthenium metathesis catalysts were incorporated into a supramolecular resorcin[4]arene capsule. Encapsulation increased catalyst stability in water-saturated toluene, delivering higher metathesis yields than the parent, non-encapsulated Hoveyda catalyst in the same reaction medium.

Olefin metathesis is now established as a core methodology in organic synthesis,[1–2] while advances in chemical biology represent an expanding interdisciplinary frontier.[3] Despite its power, however, metathesis is plagued by catalyst instability. The challenges have come to the fore with the emergence of ring-closing metathesis (RCM) in pharmaceutical manufacturing,[4] particularly process chemistry campaigns focused on the production of macrocyclic hepatitis C virus (HCV) inhibitors. Indeed, RCM is a technology of major potential importance for the production of antiviral drugs, within which macrocycles represent a fast-moving frontier.[5–8] Within this context, improving the reliability of metathesis methodologies takes on new urgency.

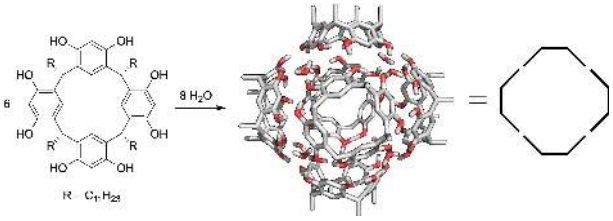
While breakthrough turnover numbers (TON) in Ru-catalyzed olefin metathesis[9] have been traced to improvements in catalyst design that inhibit unimolecular decomposition,[10] bimolecular decomposition remains a challenge.[11–15] Bimolecular degradation is operative even at ppm-level catalyst loadings,[9–10] pointing toward the merits of site-isolation (by, for example, immobilizing the molecular catalysts on a solid support).[16] To date, the problem of *induced* catalyst decomposition can be addressed only by pre-purification[4,17–18] or quenching deleterious entities as they form.[19]

Metathesis in confined environments offers an intriguing alternative approach, with the potential to address both of these challenges. Supramolecular capsules are an increasingly popular design element in homogeneous catalysis.[20–24] Encapsulation creates a second coordination sphere around the catalyst,[25–28] creating confinement effects similar to those ubiquitous in enzyme catalysis. Substrate preorganization in such confined environments[29–31] can accelerate desired intramolecular reactions, relative to intermolecular reactions.[32–35]

Within the context of olefin metathesis, catalyst confinement in porous materials[36–37] has been deployed to improve selectivity for macrocyclization over oligomerization.[38–40] To the best of our knowledge, however, encapsulation of molecular metathesis catalysts has not been explored as a strategy for stabilizing reactive intermediates against decomposition. We anticipated that encapsulation would aid in suppressing bimolecular catalyst decomposition.[11–12] Of added interest, however, is the potential capacity of the cage to protect the catalyst from attack by contaminants in the bulk solution.

Motivated by these opportunities, we sought to assess the impact of encapsulation in a resorcin[4]arene capsule[41–44] on the performance of Ru metathesis catalysts. We report the successful encapsulation of two cationic metathesis catalysts, and demonstrate that the encapsulated catalysts are more stable and productive than the leading second-generation Hoveyda catalyst (**HII**)[45] in water-saturated toluene. Here water should be recognized both as an agent of decomposition in its own right (see below), and as a model for other contaminants in the bulk reaction medium.

Formation of a stable host-guest structure requires a structural element in the catalyst that can bind to the capsule interior. Cationic guest molecules, including gold-NHC catalysts[32–33] (NHC = N-heterocyclic carbene) have been successfully incorporated within the hexameric resorcin[4]arene array (Scheme 1), via π-interactions with the internal aromatic



Scheme 1. Resorcin[4]arene molecules form hexameric capsules in water-saturated apolar solvents (toluene, benzene, CH_2Cl_2, $CHCl_3$).

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surfaces of the capsule.[42,44] Importantly, these interactions are maintained in the aromatic solvents routinely used for metathesis. We therefore considered encapsulating cationic analogues of **HII**: specifically, the trimethylammonium[46] and piperazinyl-ammonium[47] catalysts **Ru-1** and **Ru-2** (Figure 1a),[48] which we anticipated could form host-guest structures with the hexameric resorcin[4]arene capsule. A reverse ship-in-a-bottle synthesis was envisaged, involving assembly of the cage around the catalyst molecules by equilibration with the resorcin[4]arene monomers in water-saturated toluene. Of interest is the impact of encapsulation on catalyst stability in a water-rich environment. Despite successes in aqueous metathesis at high catalyst loadings,[49–50] evidence is beginning to accumulate that water exerts an unexpectedly potent negative impact on Ru-catalyzed metathesis.[51–53]

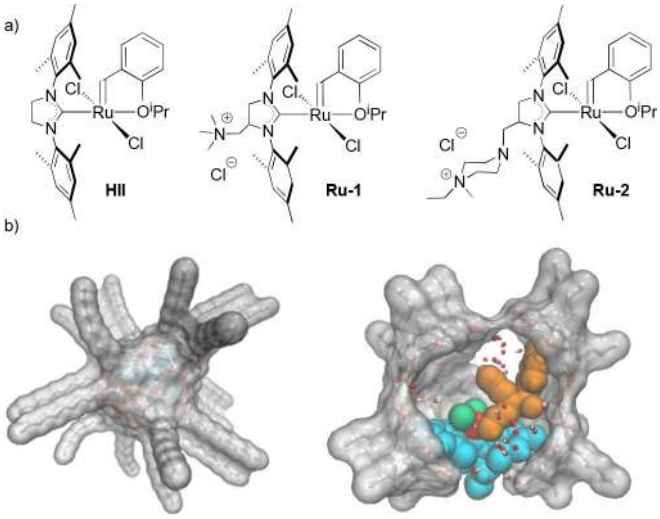
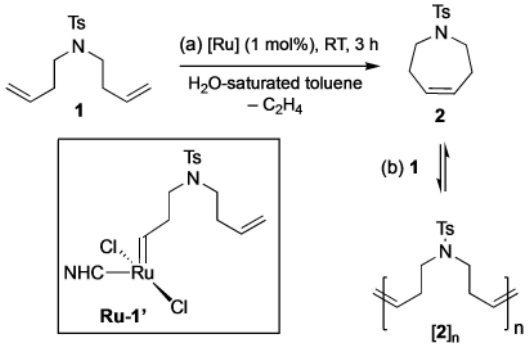


Figure 1. a) The Hoveyda catalyst **HII**, and its cationic derivatives **Ru-1** and **Ru-2**. b) Images from molecular dynamics simulations of the alkylidene intermediate **Ru-1'** (see Scheme 2) within the hexameric resorcin[4]arene capsule. Left: full model; carbon-bound hydrogen atoms and explicit solvent omitted for clarity. Right: alkyl side-chains and occluding capsule face also omitted. Gray: resorcin[4]arene; Green: Cl; Red: Ru; Blue: NHC; Orange: alkylidene ligand.



Scheme 2. a) RCM of **1** to form product **2**; b) oligomers potentially arising from intermolecular metathesis (not observed). Inset depicts the four-coordinate active alkylidene species derived from **Ru-1**, which is modelled in Figure 1b.

To confirm that the ruthenium complexes fit within the self-assembled hexameric cage, molecular dynamics simulations were carried out with **Ru-1**. As shown in Figure 1b, these demonstrate that the catalyst fits readily within the cage[54] (for details, see SI). The diffusion constant of −9.57 calculated from the dynamics simulation is in good agreement with the reported value of −9.62 for the capsule,[32,41] and the value determined experimentally below. A key feature of these self-assembled structures, relative to rigid three-dimensional cages, is facile dynamic reconfiguration of the H-bonded capsule. This permits expansion of the empty cage to accommodate entry of substrate **1** and formation of the required alkylidene intermediate (Scheme 2), as well as exit of the product.

The solvent of choice for the catalysis experiments is water-saturated toluene, both because the resorcin[4]arene capsule is known to form in this medium,[32,43] and because toluene is a standard solvent for metathesis, including in pharmaceutical manufacturing.[4] Successful encapsulation of the **Ru-1** and **Ru-2** catalysts was indicated by ^{1}H NMR and ^{1}H 2D-DOSY NMR analysis. Diffusion constants were first evaluated for the free catalysts in $CDCl_3$, as **Ru-1** and **Ru-2** are not soluble in toluene. Diffusion constants in these solvents can be compared directly, given the similarity in viscosity (0.54 vs. 0.56 mPa•s, respectively, at 25 °C).[55] Very similar diffusion constants were determined for **HII**, **Ru-1**, and **Ru-2**, with $\log_D$ values of −9.08, −9.22, and −9.10, respectively. In comparison, a $\log_D$ value of −9.57 was measured for the empty hexameric capsule. The latter, significantly lower diffusion constant reflects the much larger size of this hexameric assembly.

In the presence of the resorcin[4]arene (7.5 equiv), the diffusion constants measured for **Ru-1** and **Ru-2** were in line with those for the empty capsule (**Ru-1**, −9.52; **Ru-2**, −9.60), consistent with confinement within the cage. As typically observed for encapsulated species in these self-assembled structures,[32,42,44] a dramatic, complexation-induced upfield shift is seen for the alkylammonium ^{1}H NMR signals, confirming binding of the catalysts inside the hexameric cage (−0.9 ppm for the NMe_3 groups of **Ru-1**, vs. 3.24 for free **Ru-1**; −2.3 ppm for the NCH_2CH_3 groups of **Ru-2**, vs. 1.34 ppm for free **Ru-2**). In contrast, no change in chemical shifts is seen for **HII** under the same conditions, and its diffusion constant is essentially unaffected by the presence of the hexameric assembly ($\log_D$ −9.20; the signals for the capsule are detected separately). We infer that the cationic catalysts are encapsulated in the resorcin[4]arene cage, but that **HII** is not. This difference has important consequences for catalysis, as discussed below.

RCM of the model diene **1** (Scheme 2a) in water-saturated toluene was performed to assess the impact of encapsulation on catalyst performance, relative to **HII** as a non-encapsulated benchmark catalyst. Reaction of **HII** with **1** yielded 99% **2** over 2 h (Table 1), with no observable oligomerization (Scheme 2b).[38–39] Encapsulated **Ru-1** and **Ru-2** afforded ca. 96% **2** over the same period. A control experiment carried out with **Ru-2** in anhydrous toluene indicated no reaction, consistent with catalyst insolubility.

While these data suggest little benefit to encapsulation in terms of selectivity and productivity, a very different perspec-

Table 1. RCM of **1** by **HII** and encapsulated catalysts[a]

Catalyst[a]	Conversion[b]	RCM yield[b]
HII	99%	99%
Ru-1@resorcin[4]arene	96%	95%
Ru-2@resorcin[4]arene	99%	97%

[a]Conditions: [1] = 200 mM in water-saturated toluene, [Ru] = 1 mol% (2.0 mM), T = 20 °C, t = 2 h. For **Ru-1**, **Ru-2**, [resorcin[4]arene] = 15.0 mM. [b]GC analysis.

tive emerged when a second dose of substrate, without further catalyst, was added. Figure 2 shows the time profiles for metathesis by **HII** in both stages, relative to the corresponding reaction of **HII** in *anhydrous* toluene. In dry toluene (Figure 2a), RCM of the initial substrate charge reached 97% within 5 minutes, and was complete by the next timepoint (30 min). To test the stability of **HII**, the solution was allowed to stand for another 2.5 h before adding the second, equalivalent proportion of substrate. Consumption of **1** was slightly slower, but the RCM reaction was essentially complete within 30 min, with a turnover number (TON) of 198.

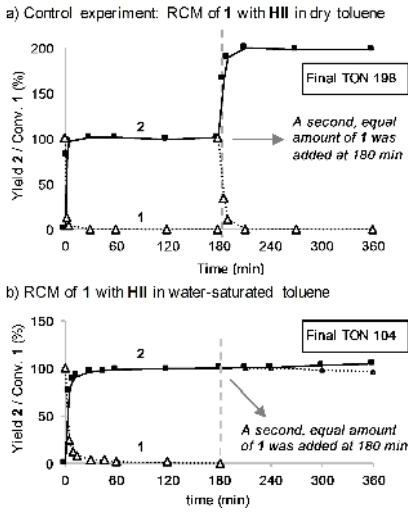


Figure 2. Rate profiles for RCM of **1** by **HII** in: a) dry toluene; b) water-saturated toluene. Conditions: [$\mathbf{1}_{initial}$] = 200 mM, [$Ru_{initial}$] = 2.0 mM. After 3 h, a second bolus of **1** was added, such that [Ru] = 1.0 mM. For details, see SI.

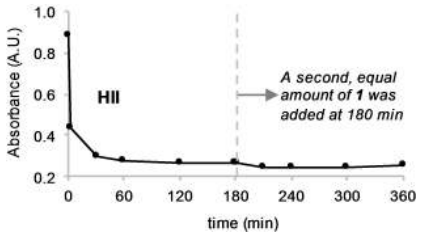


Figure 3. Rate of decrease in intensity of UV-vis absorbance band for **HII** (380 nm) during RCM of **1** in water-saturated toluene (experiment in Figure 2b).

The corresponding reaction in water-saturated toluene (Figure 2b) shows slightly slower cyclization of the initial substrate charge relative to the anhydrous reaction (75% at 5 min), although RCM was quantitative by 3 h, as expected from the data in Table 1. Following addition of a second dose of **1**, however, RCM was very sluggish, ultimately resulting in only a 4% increase in yield (total TON 104; Figure 2b). These data clearly indicate accelerated catalyst decomposition in the presence of water, consistent with the literature reports noted above.[51–53]

Catalyst decomposition was confirmed by UV-vis analysis of aliquots from the reaction in water-saturated toluene. Shown in Figure 3 is the rate of decrease in the intensity of the principal absorption band for **HII** (380 nm). An immediate, drastic drop in intensity occurred within the first 10 min of catalysis, with little further change after 30 min. Near-complete catalyst decomposition is consistent with the minimal increase in TON observed on adding the second dose of substrate.

In striking contrast, both encapsulated catalysts exhibited sustained RCM following addition of the second bolus of substrate. With **Ru-1**@resorcin[4]arene (Figure 4a), a total TON of 142 was achieved after 6 h. For **Ru-2**@resorcin[4]arene (Figure 4b), the rate of RCM is only slightly slower than that seen for free **HII** in water-saturated toluene, and the ultimate RCM yield was near-quantitative (total TON of 192). The latter value is nearly double that ultimately achieved with **HII** in „wet" toluene. We speculate that the improved performance of **Ru-2** relative to **Ru-1** may reflect the larger catalyst size. Greater constraint by the cage may increase the conformational bias toward cyclization, and/or accelerate cycloreversion of the vulnerable metallacyclobutane intermediate. Clearly, however, the cage serves to shield the catalyst (particularly **Ru-2**) from

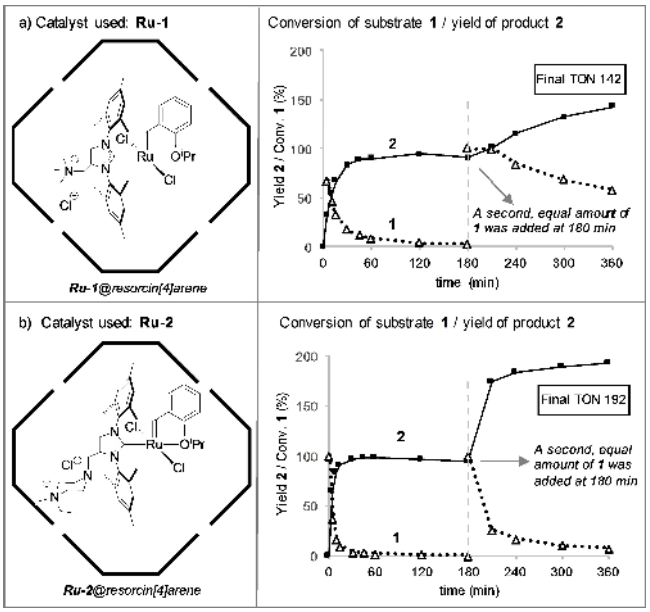


Figure 4. RCM rate profiles. a) **Ru-1**@resorcin[4]arene; b) **Ru-2**@resorcin[4]arene. Conditions as in Figure 2, with 15.0 mM resorcin[4]arene and the catalyst indicated.

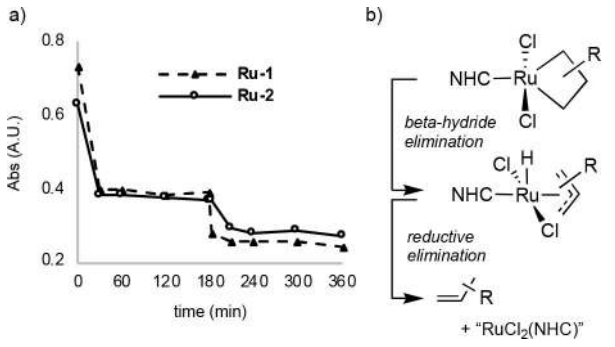


Figure 5. a) Rate profiles for decomposition of **Ru-1**@resorcin[4]arene and **Ru-2**@resorcin[4]arene, assessed by UV-vis analysis; b) unimolecular decomposition of the metallacyclobutane intermediate.

decomposition of the active species by water, as also evidenced by UV-vis analysis (Figure 5a).

Several factors may contribute to the improved lifetime of the encapsulated catalysts. First, site-isolation prevents bimolecular coupling of the [Ru]=CH_2 intermediate, an important contributor to decomposition of **HII**.[11–12] Intrinsic decomposition is then limited chiefly to β-hydride elimination from the metallacyclobutane intermediate (see Figure 5b). Second, as decomposition by water is concentration-dependent,[51–52] and the hydrophobic properties of the capsule interior are well documented,[22,32] a protective effect is anticipated from the reduced proportion of water within the capsule. Finally, confinement may exert conformational constraints that promote cyclization, as noted above, while destabilizing coordination modes that contribute to catalyst deactivation.

In conclusion, we have shown that the hexameric resorcin[4]arene capsule can be successfully used to encapsulate cationic metathesis catalysts. The encapsulated catalysts are not merely metathesis-active, but deliver turnover numbers significantly higher than the parent, uncaged catalyst **HII** in the presence of water. Improved catalyst stability is attributed, in part, to the capacity of the capsule to prevent inter-catalyst contact, and hence catalyst degradation via bimolecular coupling. In addition, however, the cage protects against attack by water, by introducing a barrier between the catalyst and the bulk, water-saturated solvent. Site-isolation, notwithstanding its importance, has long been attainable via established surface-anchoring methods. The additional capacity of the cage to shield the catalyst against attack by deleterious agents in the solvent medium represents a unique advantage now under further study.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: catalyst encapsulation · metathesis · supramolecular chemistry · ruthenium-catalyzed metathesis · homogeneous catalysis

[1] R. H. Grubbs, A. G. Wenzel, *Handbook of Metathesis*, 2nd ed. Wiley-VCH, Weinheim, **2015**.
[2] K. Grela, *Olefin Metathesis-Theory and Practice* Wiley, Hoboken, NJ, **2014**.
[3] a) B. Bhushan, Y. A. Lin, M. Bak, A. Phanumartwiwath, N. Yang, M. K. Bilyard, T. Tanaka, K. L. Hudson, L. Lercher, M. Stegmann, S. Mohammed, B. G. Davis, *J. Am. Chem. Soc.* **2018**, *140*, 14599–14603; b) X. Lu, L. Fan, C. B. Phelps, C. P. Davie, C. P. Donahue, *Bioconjugate Chem.* **2017**, *28*, 1625–1629; c) C. M. Grison, G. M. Burslem, J. A. Miles, L. K. A. Pilsl, D. J. Yeo, Z. Imani, S. L. Warriner, M. E. Webb, A. J. Wilson, *Chem. Sci.* **2017**, *8*, 5166–5171; d) P. M. Cromm, J. Spiegel, P. Kuchler, L. Dietrich, J. Kriegesmann, M. Wendt, R. S. Goody, H. Waldmann, T. N. Grossmann, *ACS Chem. Biol.* **2016**, *11*, 2375–2382; e) J. B. Binder, R. T. Raines, *Curr. Opin. Chem. Biol.* **2008**, *12*, 767–773.
[4] a) C. S. Higman, J. A. M. Lummiss, D. E. Fogg, *Angew. Chem. Int. Ed.* **2016**, *55*, 3552–3565; *Angew. Chem.* **2016**, *128*, 3612–326; b) V. Farina, A. Horváth, in *Handbook of Metathesis*, Vol. 2 (Eds.: R. H. Grubbs, A. G. Wenzel), Wiley-VCH, Weinheim, **2015**, pp. 633–658; c) K. R. Fandrick, J. Savoie, N. Y. Jinhua, J. J. Song, C. H. Senanayake, in *Olefin Metathesis – Theory and Practice* (Ed.: K. Grela), Wiley, Hoboken, **2014**, pp. 349–366.
[5] E. Marsault, M. L. Peterson, *J. Med. Chem.* **2011**, *54*, 1961–2004.
[6] F. Giordanetto, J. Kihlberg, *J. Med. Chem.* **2014**, *57*, 278–295.
[7] E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug Discovery* **2008**, *7*, 608–624.
[8] K.-O. Chang, Y. Kim, S. Lovell, A. D. Rathnayake, W. C. Groutas, *Viruses* **2019**, *11*, 197.
[9] a) V. M. Marx, A. H. Sullivan, M. Melaimi, S. C. Virgil, B. K. Keitz, D. S. Weinberger, G. Bertrand, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2015**, *54*, 1919–1923; b) R. Gawin, A. Tracz, M. Chwalba, A. Kozakiewicz, B. Trzaskowski, K. Skowerski, *ACS Catal.* **2017**, *7*, 5443–5449; c) R. Gawin, A. Kozakiewicz, P. A. Guńka, P. Dąbrowski, K. Skowerski, *Angew. Chem. Int. Ed.* **2017**, *56*, 981–986; d) D. L. Nascimento, A. Gawin, R. Gawin, P. A. Guńka, J. Zachara, K. Skowerski, D. E. Fogg, *J. Am. Chem. Soc.* **2019**, *141*, 10626–10631.
[10] D. L. Nascimento, D. E. Fogg, *J. Am. Chem. Soc.* **2019**, *141*, 19236–19240.
[11] G. A. Bailey, M. Foscato, C. S. Higman, C. S. Day, V. R. Jensen, D. E. Fogg, *J. Am. Chem. Soc.* **2018**, *140*, 6931–6944.
[12] V. Thiel, K.-J. Wannowius, C. Wolff, C. M. Thiele, H. Plenio, *Chem. Eur. J.* **2013**, *19*, 16403–16414.
[13] T. S. Pilyugina, R. R. Schrock, A. S. Hock, P. Muller, *Organometallics* **2005**, *24*, 1929–1937.
[14] L. P. H. Lopez, R. R. Schrock, P. Muller, *Organometallics* **2006**, *25*, 1978–1986.
[15] W. C. P. Tsang, R. R. Schrock, A. H. Hoveyda, *Organometallics* **2001**, *20*, 5658–5669.
[16] For comprehensive overviews of strategies employed in immobilizing molecular olefin metathesis catalysts, see: a) A. Dewaele, F. Verpoort, B. Sels, *ChemCatChem* **2016**, *8*, 3010–3030; b) C. Coperet, J. M. Basset, *Adv. Synth. Catal.* **2007**, *349*, 78–92; c) M. R. Buchmeiser, in *Olefin Metathesis-Theory and Practice* (Ed.: K. Grela), Wiley, Hoboken, NJ, **2014**, pp. 495–514; For a discussion of challenges, particularly in terms of productivity and leaching from the support, see:; d) S. Hubner, J. G. de Vries, V. Farina, *Adv. Synth. Catal.* **2016**, *358*, 3–25.
[17] C. Lübbe, A. Dumrath, H. Neumann, M. Schäffer, R. Zimmermann, M. Beller, R. Kadyrov, *ChemCatChem* **2014**, *6*, 684–688.
[18] R. Kadyrov, *Chem. Eur. J.* **2013**, *19*, 1002–1012.
[19] A. G. Santos, G. A. Bailey, E. N. dos Santos, D. E. Fogg, *ACS Catal.* **2017**, *7*, 3181–3189.
[20] C. M. Hong, R. G. Bergman, K. N. Raymond, F. D. Toste, *Acc. Chem. Res.* **2018** *51*, 2447–2455.
[21] C. J. Brown, F. D. Toste, R. G. Bergman, K. N. Raymond, *Chem. Rev.* **2015**, *115*, 3012–3035.
[22] L. Catti, Q. Zhang, K. Tiefenbacher, *Chem. Eur. J.* **2016**, *22*, 9060–9066.

[23] M. J. Wiester, P. A. Ulmann, C. A. Mirkin, *Angew. Chem. Int. Ed.* **2011**, *50*, 114–137.
[24] Q. Zhang, L. Catti, K. Tiefenbacher, *Acc. Chem. Res.* **2018**, *51*, 2107–2114.
[25] S. H. A. M. Leenders, R. Gramage-Doria, B. de Bruin, J. N. H. Reek, *Chem. Soc. Rev.* **2015**, *44*, 433–448.
[26] M. Raynal, P. Ballester, A. Vidal-Ferran, P. W. N. M. Van Leeuwen, *Chem. Soc. Rev.* **2014**, *43*, 660–1733.
[27] M. Raynal, P. Ballester, A. Vidal-Ferran, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.* **2014**, *43*, 1734–1787.
[28] L. J. Jongkind, X. Caumes, A. P. T. Hartendorp, J. N. H. Reek, *Acc. Chem. Res.* **2018**, *51*, 2115–2128.
[29] J. Meeuwissen, J. N. H. Reek, *Nat. Chem.* **2010**, *2*, 615–621.
[30] T. S. Koblenz, J. Wassenaar, J. N. H. Reek, *Chem. Soc. Rev.* **2008**, *37*, 247–262.
[31] M. Yoshizawa, J. K. Klosterman, M. Fujita, *Angew. Chem. Int. Ed.* **2009**, *48*, 3418–3438.
[32] a) A. Cavarzan, A. Scarso, P. Sgarbossa, G. Strukul, J. N. H. Reek, *J. Am. Chem. Soc.* **2011**, *133*, 2848–2851; b) A. C. H. Jans, A. Gómez-Suárez, S. P. Nolan, J. N. H. Reek, *Chem. Eur. J.* **2016**, *22*, 14836–14839; c) L. Adriaenssens, A. Escribano-Cuesta, A. Homs, A. M. Echavarren, P. Ballester, *Eur. J. Org. Chem.* **2013**, 1494–1500.
[33] For a review on gold catalysis in capsules, see: A. C. H. Jans, X. Caumes, J. N. H. Reek, *ChemCatChem.* **2019**, *11*, 287–297.
[34] Z. J. Wang, C. J. Brown, R. G. Bergman, K. N. Raymond, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 7358–7360.
[35] Q. Q. Wang, S. Gonell, S. H. A. M. Leenders, M. Dürr, I. Ivanovic-Burmazovic, J. N. H. Reek, *Nat. Chem.* **2016**, *8*, 225–230.
[36] F. Ziegler, J. Teske, I. Elser, M. Dyballa, W. Frey, H. Kraus, N. Hansen, J. Rybka, U. Tallarek, M. R. Buchmeiser, *J. Am. Chem. Soc.* **2019**, *141*, 19014–19022.
[37] J.-E. Jee, J. L. Cheong, J. Lim, C. Chen, S. H. Hong, S. S. Lee, *J. Org. Chem.* **2013**, *78*, 3048–3056.
[38] J. C. Conrad, M. D. Eelman, J. A. Duarte Silva, S. Monfette, H. H. Parnas, J. L. Snelgrove, D. E. Fogg, *J. Am. Chem. Soc.* **2007**, *129*, 1024–1025.
[39] S. Monfette, D. E. Fogg, *Chem. Rev.* **2009**, *109*, 3783–3816.
[40] Alternatively, macrocyclic lactones have been distilled from the reaction mixture as they form. See: A. Sytniczuk, M. Dąbrowski, Ł. Banach, M. Urban, S. Czarnocka-Śniadała, M. Milewski, A. Kajetanowicz, K. Grela, *J. Am. Chem. Soc.* **2018**, *40*, 8895–8901.
[41] a) L. Avram, Y. Cohen, *J. Am. Chem. Soc.* **2002**, *124*, 15148–15149; b) L. Avram, Y. Cohen, *Org. Lett.* **2002**, *4*, 4365–4368.
[42] a) A. Shivanyuk, J. Rebek, *Proc. Mont. Acad. Sci.* **2001**, *98*, 7662–7665; b) N. K. Beyeh, M. Kogej, A. Åhman, K. Rissanen, C. A. Schalley, *Angew. Chem. Int. Ed.* **2006**, *45*, 5214–5218.
[43] J. J. L. Atwood, L. R. MacGillivray, *Nature* **1997**, *389*, 469–472.
[44] For a review on the applications of hexameric resorcinarene capsules in catalysis, see: C. Gaeta, C. Talotta, M. De Rosa, P. La Manna, A. Soriente, P. Neri, *Chem. Eur. J.* **2019**, *25*, 4899–4913.
[45] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
[46] K. Skowerski, C. Wierzbicka, G. Szczepaniak, Ł. Gułajski, M. Bienieka, K. Grela, *Green Chem.* **2012**, *14*, 3264–3268.
[47] K. Skowerski, G. Szczepaniak, C. Wierzbicka, L. Gulajski, M. Bieniek, K. Grela, *Catal. Sci. Technol.* **2012**, *2*, 2424–2427.
[48] For a recent review, including alternative immobilization strategies deployed with these catalysts, see: T. K. Olszewski, M. Bieniek, K. Skowerski, *Org. Process Res. Dev.* **2020**, *24*, 125–145.
[49] B. H. Lipshutz, S. Ghorai, in *Olefin Metathesis – Theory and Practice* (Ed.: K. Grela), **2014**, pp. 515–521.
[50] K. Grela, L. Gulajski, K. Skowerski, in *Metal-Catalyzed Reactions in Water* (Eds.: P. H. Dixneuf, V. Cadierno), Wiley-VCH, Weinheim, **2013**, pp. 291–336.
[51] S. Guidone, O. Songis, F. Nahra, C. S. J. Cazin, *ACS Catal.* **2015**, *5*, 2697–2701.
[52] W. L. McClennan, S. A. Rufh, J. A. M. Lummiss, D. E. Fogg, *J. Am. Chem. Soc.* **2016**, *138*, 14668–14677.
[53] S. J. Ton, D. E. Fogg, *ACS Catal.* **2019**, *9*, 11329–11334.
[54] Rebek's well-documented 55% rule (see: S. Mecozzi, J. Rebek, *Chem. Eur. J.* **1998**, *4*, 1016–1022) states that the optimum guest volume is 55% of the cage volume (although smaller or larger guests can be accommodated). The H-bonded nature of the resorcinarene cage renders its volume and shape somewhat dynamic, as noted in the text. The calculated volume of the free cage is ca. 1300 A^3, vs. 540 A^3 for **Ru-1** (ca. 42%). The volume of the catalyst-substrate complex is 864 A^3, and the volume of the expanded cage when accommodating this complex is 1900 A^3, thus near the optimum volume according Rebek's Rule.
[55] W. M. Haynes, *CRC Handbook of Chemistry and Physics*, 95th ed. (CRC Press, Boca Raton, FL, **2014**.

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