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Metathesis in Pure Water Mediated by Supramolecular Additives

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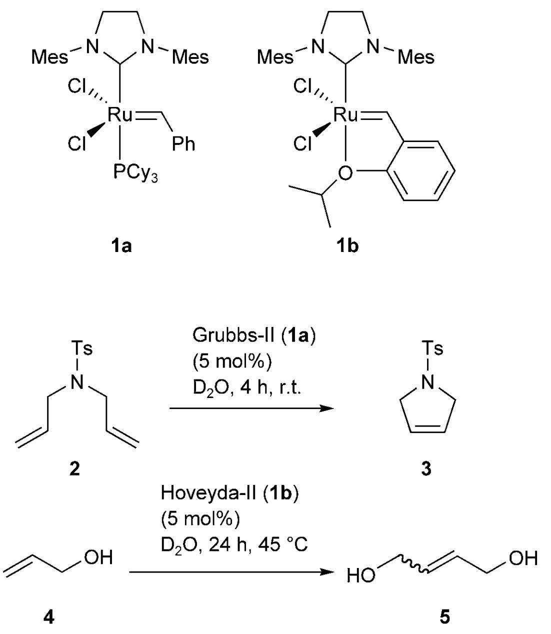
Abstract: Supramolecular, water-soluble additives based on calix[*n*]arenes exhibit a beneficial influence on the ring-closing and cross metathesis of non-polar substrates in pure aqueous medium using standard Grubbs-II and Hoveyda-II catalysts. The catalytic activity observed in water is virtually the same as that in pure methanol. Quantitative yields of metathesis product can be achieved under mild aerobic conditions in/on water by (micro)solubilization of both the catalyst and starting materials by the macrocycles.

Keywords: calixarenes; green chemistry; metathesis; supramolecular chemistry; water

In recent years, alkene metathesis has developed to a very valuable, reliable, and widely used methodology, which has significantly increased the organic chemists "synthetic tool-box".[1] Although at a very high stage of development, there is still a considerable necessity for improved methods in terms of more efficient catalysts,[2] or novel, sustainable concepts.[3]

Many target molecules of biological relevance are mainly soluble in aqueous solution. Therefore, there is a substantial interest in methodologies for aqueous metal organic chemistry[4] and especially Grubbs-type reactions.[5] Here, previous studies have focused on the design of water-soluble Grubbs-type catalysts,[6] polymer-,[7] or membrane-bound catalytic systems,[8] and catalysts bearing PEGylated ligands.[9] Moreover, ring-closing metathesis (RCM) has been successfully carried out in non-conventional media or micellar solution.[10,11]

Even catalysis in aqueous media is possible just by the use of commercially available Grubbs (**1a**) and Hoveyda catalysts (**1b**) (Scheme 1).[12,13] However, reasonable yields are still only available in those cases where co-solvents such as DME or acetone are added to a high extent.[14]

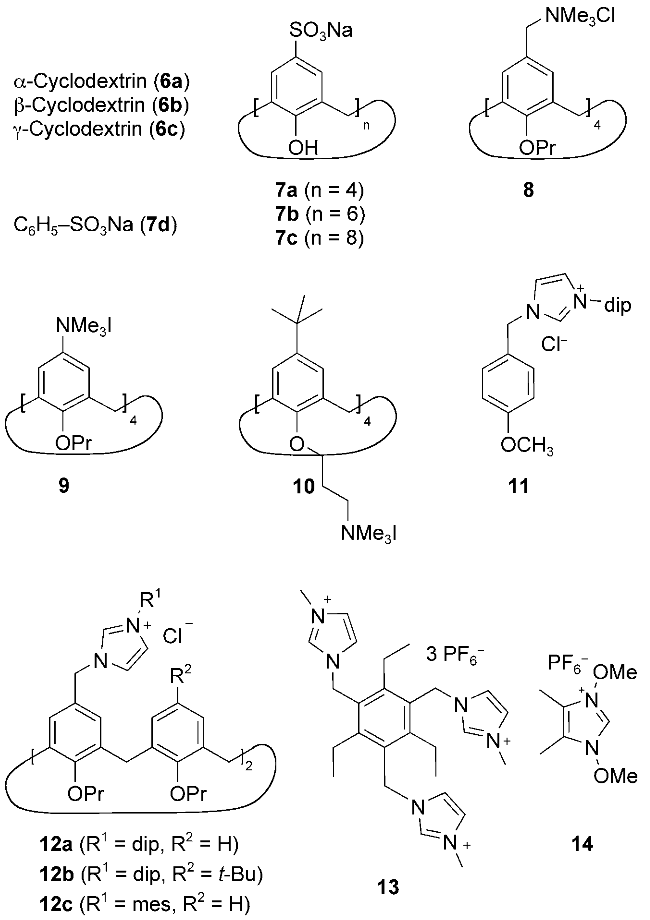


Scheme 1. Used catalysts and test reactions.

In a previous study we could show that water-soluble macrocycles can enhance the efficiency of Suzuki coupling reactions of aryl chlorides in pure water without hampering preparative features such as extraction of organic, non-polar products from the aqueous phase. Therefore, we intended to explore this family of compounds for use in metathesis applications.[15] Especially sulfonato- and imidazolio-calix[*n*]arenes are tested as additives (Scheme 2) for ring-closing and cross metathesis (CM) (Scheme 1).[16,17]

Two major problems must be overcome for efficient olefin metathesis in aqueous solution: decomposition of the catalytic species,[18] and the low solubility of both the catalysts **1a** or **1b**, respectively, and the olefinic substrates.

To test the influence of supramolecular additives onto the RCM of tosylamine **2** under standard conditions, ammonium calixarene **8**, calixarene **12a**, the non-cyclic compound **11**, and sulfonated calix-



Scheme 2. Used additives for the RCM to yield **3** and **5**, respectively (dip = 2,6-diisopropylphenyl).

[6,8]arenes **7b**, **c** were added to all reaction components in MeOH-d_4 as an organic solvent (Scheme 2). Using the highly active Hoveyda–Grubbs-II catalyst (**1b**) nearly no influence on the catalytic activity could be observed. In all cases after 4 h yields well above 90% were observed. Surprisingly, in case of the standard Grubbs-II catalyst **1a** the RCM of **2** is retarded by the cationic species **8** and **11** (Table 1, entries 4 and 5) and calixarene **12a** (entry 6) and nearly totally inhibited using sulfonated calix[6,8]arenes **7b**, **c** (<3% yield of RCM product, entries 2 and 3)! Here, one might assume a ligation of the catalytic species by the sulfonate anion reducing the catalytic ability.

The activity of Grubbs catalyst **1a** in different solvent mixtures has been briefly explored as shown in Table 1 (entries 1, 7, and 8). These observations are in line with data obtained by Blechert and co-workers for the metathesis in methanol and methanol/water mixtures indicating that the catalytic ability is regained with increasing water content.[19] Using water as sole solvent, basically the same catalytic performance can be observed as in pure methanol. These findings intrigued us to perform all further experiments using supramolecular additives in pure water instead of mixtures.

Pure aqueous solutions, containing 5 mol% additive, served as reaction media for RCM as well as CM reactions (Table 2, Figure 1 and Figure 2). In first experiments, it was found that casual shaking of the reaction vessels yields tend to be somewhat lower than yields obtained by stirring at rates 1000–1400 min^{-1}. Therefore, all reactions mixtures were stirred at a constant stirring rate of 1000 min^{-1} unless otherwise stated.

Table 1. Yields of the RCM of **2** using Grubbs-II catalyst **1a** (5 mol%).[a]

Entry	Solvent	Additive	Yield **3** [%]
1	MeOD	–	79
2[b]	MeOD	**7b**	<3
3[b]	MeOD	**7c**	<3
4[b]	MeOD	**8**	54
5[b]	MeOD	**11**	56
6[b]	MeOD	**12a**	38
7	MeOD/D_2O (1:1)	–	36
8	D_2O	–	75

[a] *Reaction conditions:* 4 h and room temperature, 5 mol% catalyst and additive.

[b] Reaction mixture was shaken hourly for 30 seconds and was placed directly in an NMR tube to determine the conversion.

Table 2. Yields and *E*/*Z* ratio for metathesis reactions in water.[a]

Entry	Additive	Yield **3** [%]	Yield **5** [%]	*E*/*Z* ratio (**5**)
1	–	75	44	16:1
2	**6a**	n.d.[b]	31	17:1
3	**6b**	72	39	20:1
4	**6c**	35	27	15:1
5	**7a**	99	26	12:1
6	**7b**	99	24	16:1
7	**7c**	99	23	18:1
8	**7d**[c]	90	37	14:1
9	**8**	45	50	18:1
10	**9**	44	36	16:1
11	**10**	60	30	13:1
12	**11**	18	26	16:1
13	**12a**	11	54	21:1
14	**12b**	12	24	15:1
15	**12c**	9	49	22:1
16	**13**	30	24	28:1
17	**14**	86	14	11:1

[a] *Reaction conditions:* for **3**: 4 h, room temperature, catalyst = Grubbs-II (**1a**); for **5**: 24 h, 45 °C, catalyst = Hoveda-II (**1b**); in all cases 5 mol% catalyst and additive. Errors in yields are usually <2%.

[b] Not detected owing to signal overlap of cyclodextrin and starting material.

[c] 30 mol% additive.

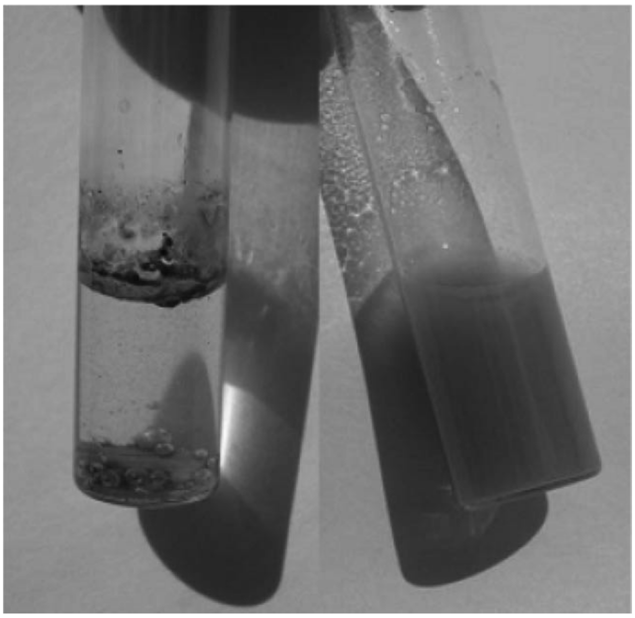


Figure 1. Reaction vials without any additive (*left*), with sulfocalix[6]arene **7b** (*right*).

Surprisingly, we found the highest conversions of 99% using sulfocalixarenes **7a–c** as additives, possibly because of the beneficial influence of (micro)solubilization of organic compounds, whereas without additive, only 75% RCM product **3** was observed. The addition of sulfocalixarenes enhances both the catalytic activity and solubility of the catalyst in polar media.

This advantageous effect is also visible, because the reaction is no longer heterogeneous, but becomes pseudo-homogeneous (Figure 1). It is noteworthy that because of "cavity effects" sulfocalixarenes are actually somewhat superior additives than the monomeric building block, benzenesulfonate **7d**. Compared to the RCM without any additives, we observed that adding 5 mol% of the hydroxyimidazolium 3-oxide salt **14** also led to higher conversions for **2**→**3** (86%). However, this positive effect is reversed using the Hoveyda-II (**1b**, 14% yield **5**) instead of the Grubbs-II catalyst (**1a**). To the best of our knowledge, this is the first example where such oxy-imidazolium salts – potential precursors for N-heterocyclic carbenes – are used in metathesis reactions.[20] Currently, we are trying to synthesize Grubbs-type catalysts containing NHCs based on hydroxyimidazolium 3-oxides to test whether such ruthenium complexes exhibit inherently higher catalytic activity and to gain a deeper insight into these novel NHC precursors.

In contrast to RCM reactions, where anionic, sulfonated calix[*n*]arenes were the additive of choice, the highest levels of conversion in CM reactions could be

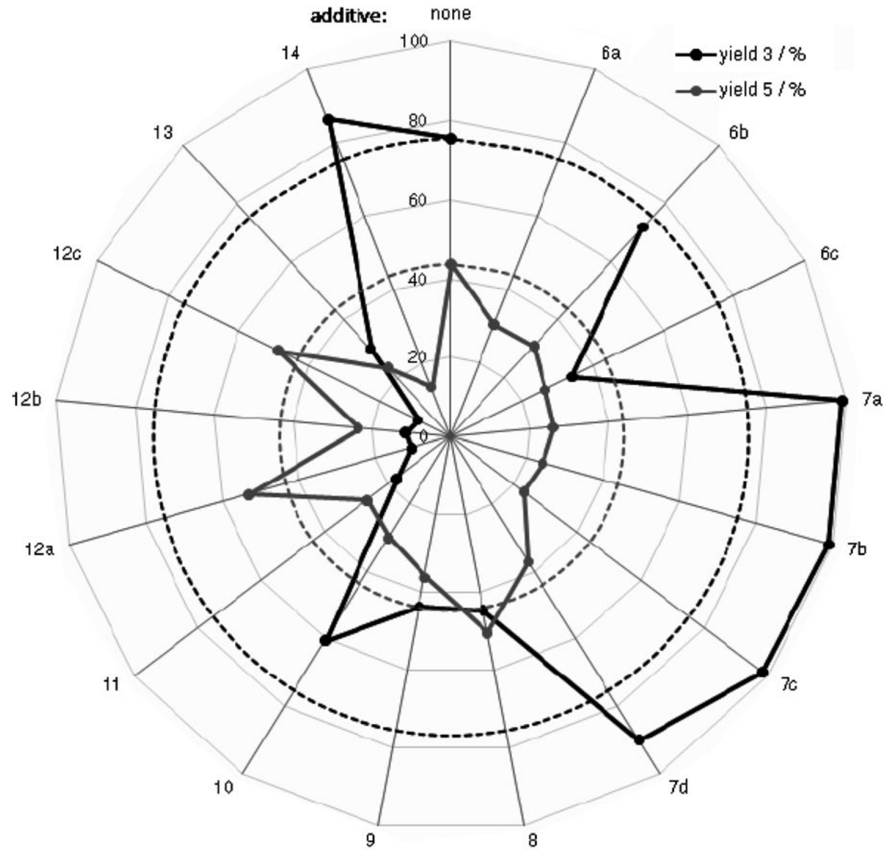
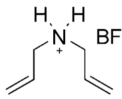


Figure 2. Yields for metathesis reactions.

observed with cationic, imidazolio-substituted calixarenes **12a**/**12c** or with the ammonium calixarene **8**. The achieved higher conversion, when adding **12a** or **12c** in comparison to the open-chain compound **11** indicates that cavity effects are not insignificant. This is also mirrored by the influence of these additives onto the *E/Z* ratio. Instead of a *ca.* 15:1 ratio observed without or with open chain additives **7d**, **11** (Table 2, entries 8 and 12), imidazoliocalix[4]arenes enhance the formation of the linear *E*-isomer up to an *E/Z* ratio of *ca.* 22:1. Furthermore, it was found that the formation of homodimer **5** was less favoured when adding **12b**, presumably due to steric effects.

In a search for efficient water-soluble substrates we have tested the compounds **15**–**17** (Table 3), mostly using the more active catalyst **1b**. Unfortunately as already indicated by other literature precedents,[6b–c,7a] which used higher substrate concentrations and longer reaction times to get low to mediocre yields, these RCM substrates gave only minimal (yields 3–10%) or no reaction under our reaction conditions with or without supramolecular additives.

Table 3. RCM of water-soluble substrates **15**, **16** and **17** in D_2O.[a]



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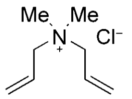

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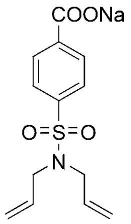

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Entry	Substrate	Cat.	*T* [°C]	Additive	Yield [%]
1	**15**	**1b**	45	–	<3
2	**15**	**1b**	65	**7b**	<3
3	**15**	**1a**	45	**7b**	<3
4	**15**	**1b**	45	**7c**	<3
5	**15**	**1b**	45	**14**	<3
6	**16**	**1b**	45	–	<3
7	**16**	**1b**	65	**7b**	<3
8	**17**	**1b**	r.t.	–	4
9	**17**	**1b**	45	–	11

[a] *Reaction conditions:* 5 mol% catalyst and additive, D_2O, 24 h, $c_{\text{substrate}} = 0.05\,\text{M}$.

In summary, we have demonstrated that commercially available catalysts **1a**/**1b** can efficiently promote metathesis reactions in pure water without any need for degassing or an inert atmosphere. Supramolecular additives, which have cavities large enough to accommodated substituted phenyl rings,[21] can have significant advantageous effects on the metathesis. When adding for example, sulfocalix[*n*]arenes the RCM in water can be carried out using the standard Grubbs-II catalyst under very mild, aerobic conditions with high levels of conversion!

Experimental Section

Representative Procedures for Metathesis Reactions in D_2O

RCM of 2: A mixture of the catalyst **1a** (1.90 μmol, 5 mol%), a supramolecular additive (1.90 μmol, 5 mol% to substrate), when applicable, and the substrate **2** (38 μmol) in 850 μL D_2O as the solvent was stirred for 4 h at room temperature at a constant stirring rate of 1400 min^{-1}. An aliquot (150–200 μL) was withdrawn, diluted with MeOD to 600 μL, and directly analyzed by ^{1}H NMR spectroscopy.

CM of 4: A mixture of the catalyst **1b** (6.38 μmol, 5 mol%), a supramolecular additive (6.38 μmol, 5 mol% to substrate), when applicable, and allylic alcohol (128 μmol) in 850 μL D_2O as the solvent was stirred for 24 h at 45 °C at a constant stirring rate of 1000 min^{-1}. After 24 h, the reaction mixture was placed in an NMR tube and the conversion was determined by ^{1}H NMR spectroscopy.

All yields and *E/Z* ratios reported were reproduced 2–5 times and the yields determined by NMR spectroscopy correlate reasonably with yields obtained in conventionally worked-up runs.

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