

## Practical Olefin Metathesis in Protic Media under an Air Atmosphere

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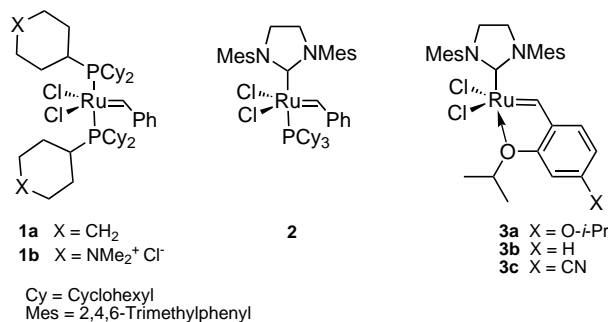
**Abstract:** The discovery that efficient olefin metathesis reactions involving previously challenging terminal olefin substrates are possible using novel and readily available catalyst systems in non-distilled, non-degassed protic media in air is reported.

**Keywords:** catalysis; metathesis; olefins; ruthenium; water

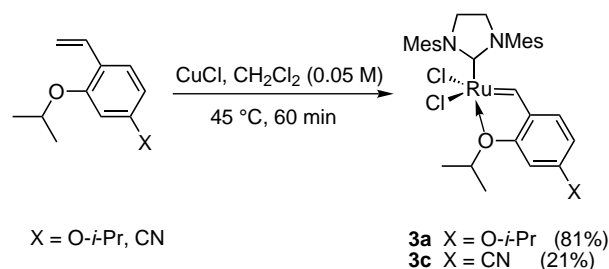
Olefin metathesis has recently risen to prominence as one of the most powerful tools for the formation of carbon-carbon bonds under mild conditions.<sup>[1]</sup> This is primarily due to the development of catalysts such as **1a** and **2** (Figure 1), which combine excellent functional group tolerance with high catalytic activity.<sup>[2,3]</sup>

Nevertheless, due to concerns regarding the catalyst-deactivating effects of oxygen and moisture, olefin metathesis reactions are conducted almost exclusively in aprotic, dry organic solvents under a protective inert atmosphere.<sup>[4]</sup> It is therefore perhaps not surprising, despite the potential benefits both from an environmental and biomolecule synthesis point of view, that the application of well-defined olefin metathesis catalysts in protic solvent systems (particularly aqueous media), has not been widespread. Pioneering work from the Grubbs group demonstrated that water-soluble polar catalysts such as **1b** could promote ring-opening metathesis

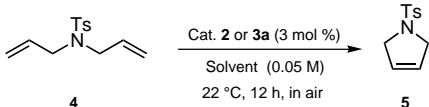
polymerisation (ROMP) and ring-closing metathesis (RCM) reactions in water and methanol.<sup>[5]</sup> However, **1b** was found to be highly oxygen sensitive; requiring manipulation and storage under an inert atmosphere, and rigorous degassing of reaction solvents was essential. In addition, **1b** and similar analogues<sup>[5d,f]</sup> were incompatible with simple  $\alpha,\omega$ -heptadiene RCM substrates (one internal olefin component was necessary) and it also proved almost completely inactive in cross-metathesis (CM) reactions. We have been recently investigating the properties of alkylidene **3b**, which is a somewhat slower initiator than **2**, but which has a stability high enough to allow it to outperform other alkylidenes in certain cases where catalyst decomposition is critical.<sup>[6]</sup> A polymer-bound version of **3b** has recently been shown to be active in water and methanol.<sup>[7]</sup> Recently, Grubbs has developed a sulphone-substituted analogue of **1a** for use in various protic and aprotic solvent systems,<sup>[5f]</sup> and thus given our interest in this field,<sup>[7]</sup> and with the aim of widening the reaction scope, we were prompted to report our results concerning the use of conventional alkylidenes (such as **2** and **3**). These catalysts benefit from the extra stability conferred by the *N*-heterocyclic carbene (NHC) ligand,<sup>[2b,3,8]</sup> in metathesis reactions in various protic media under conditions where **1b** and related catalysts<sup>[5a–f]</sup> are expected to fail, i.e., terminal olefin substrates under an air atmosphere in non-degassed and undistilled solvents. To test the effect of benzyldiene electrophilicity on catalyst efficiency in nucleophilic protic media, novel alkoxy- and cyano-substituted catalysts **3a** and **3c**, respectively, were prepared from the corresponding styrenes (Scheme 1) using standard procedures.<sup>[8]</sup> The



**Figure 1.** Olefin metathesis catalysts.



**Scheme 1.** Synthesis of pre-catalysts **3a** and **3c**.

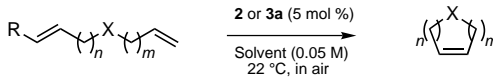
**Table 1.** RCM of **4** in undistilled protic solvents in air using pre-catalysts **2** and **3a**.


Solvent	Conversion [%] <sup>[a]</sup>	
	Cat. <b>2</b>	Cat. <b>3a</b>
MeOH	94	96 <sup>[c]</sup>
MeOH/H <sub>2</sub> O (3:1)	29	87
MeOH/H <sub>2</sub> O (1:1) <sup>[b]</sup>	54	90
MeOH/H <sub>2</sub> O (1:3) <sup>[b]</sup>	77	94
DMF	95 <sup>[c]</sup>	96 <sup>[c]</sup>
DMF/H <sub>2</sub> O (3:1)	91	72 <sup>[c]</sup>
DMF/H <sub>2</sub> O (1:1)	29	68
DMF/H <sub>2</sub> O (1:3) <sup>[b]</sup>	82	94

<sup>[a]</sup> Determined by <sup>1</sup>H NMR spectroscopy.<sup>[b]</sup> Substrate not miscible with solvent.<sup>[c]</sup> Catalyst initially soluble.

results of our initial RCM experiments are outlined in Table 1.

The RCM of terminal olefin diene **4** in various solvent mixtures produced unexpected results. First, pre-catalyst **2**, which is largely insoluble in MeOH, was found to be active in this solvent over time,<sup>[9]</sup> with nearly quantitative conversion of the substrate possible using modest catalyst loading. In methanol-water mixtures however, conversion falls sharply until enough water is present such that the substrate is no longer miscible (i.e., 50% H<sub>2</sub>O), whereupon reaction efficiency improves again. This observation is consistent with homogeneous catalysis occurring in the liquid substrate and not the bulk aqueous media, and as such may be comparable to emulsion conditions.<sup>[10]</sup> Benchmark catalyst **2** was also found to be highly active (and soluble) in DMF, and could even tolerate 25% H<sub>2</sub>O without a significant loss of activity. Phosphane-free alkylidenes of general type **3**, which are soluble in MeOH (**3b** only sparingly), also gave interesting results. The more stable,<sup>[11]</sup> electron-rich **3a** was a remarkably more efficient catalyst under the conditions employed than its more electron-deficient analogues **3b** and **3c**, which gave only 60 and 20% conversion, respectively, for the RCM of **4** in MeOH. This is noteworthy, as **3c** is comparable in terms of initiation rates to the most efficacious pre-catalysts developed in our laboratories for RCM in CH<sub>2</sub>Cl<sub>2</sub>.<sup>[12]</sup> We would postulate that the fast generation of a relatively large amount of catalytically active species results in rapid decomposition in nucleophilic protic solvents. In addition to exhibiting impressive activity in methanol and DMF, using **3a** conversion did not drop dramatically in aqueous media, instead a gradual decline in catalyst efficacy with increasing water content was observed. In cases where the substrate was miscible in aqueous

**Table 2.** RCM of substrates **6–10** using pre-catalysts **2** and **3a**.


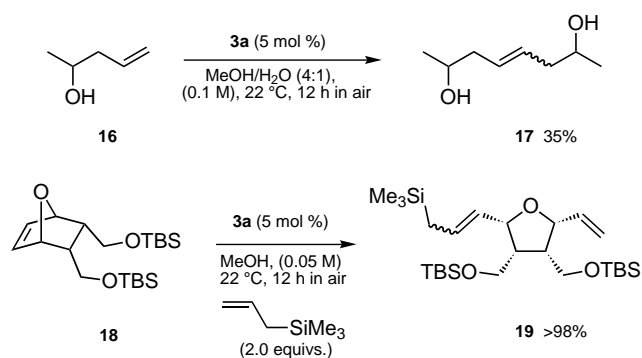
Solvent	Substrate	Catalyst	Conversion [%] <sup>[a]</sup>
MeOH	<b>6</b>	<b>2</b>	> 98
MeOH	<b>7</b>	<b>2</b>	74
MeOH	<b>8</b>	<b>2</b>	> 98
MeOH	<b>9</b>	<b>2</b>	> 98
MeOH	<b>10</b>	<b>2</b>	89
MeOH/H <sub>2</sub> O (4:1) <sup>[b]</sup>	<b>8</b>	<b>3a</b>	> 98
MeOH/H <sub>2</sub> O (4:1) <sup>[b]</sup>	<b>9</b>	<b>3a</b>	> 98

<sup>[a]</sup> Determined by <sup>1</sup>H NMR spectroscopy.<sup>[b]</sup> Reaction at 45 °C.

media, **3a** generally gave better results than **2**. This could be partially ascribed to a greater solubility over time in aqueous solvent mixtures, allowing more pre-catalyst to come in contact with the substrate.<sup>[13]</sup> The superiority of **3a** over **3b, c** can be rationalised in terms of slower initiation rates and greater pre-catalyst stability in nucleophilic solvents, presumably a consequence of the relatively electron rich Ru=C bond in **3a**.<sup>[11,12c]</sup> It is interesting to note that **1a** is also active in methanol under these conditions,<sup>[5d]</sup> although higher catalyst loadings (5 mol %) were required to give 85% conversion of **4** to heterocycle **5**.

With these results in hand, it was decided to test the compatibility of **2** and **3a** with more challenging substrates in protic media. Since both catalysts ring-close **4** in methanol with similar ease, only the parent catalyst **2** was tested in this solvent. It was gratifying to find that the smooth formation of 5-, 7-, and 8-membered rings (**11–15**) in non-degassed, undistilled methanol under an air atmosphere was possible using **2** (Table 2). The potential utility of **3a** in homogeneous aqueous media was further underlined by the efficient conversion of **8** and **9** to **13** and **14**, respectively, in methanol-water (4:1). It is important to note that while at room-temperature these reactions are clean, the use of elevated temperatures (with the exception of reactions involving **8**) results in rapid catalyst decomposition and subsequent formation of significant levels of cyclic and acyclic isomerisation products.<sup>[7]</sup>

The most difficult olefin metathesis process in protic media is CM, where the intermediate alkylidene lifetimes required for intermolecular reaction are often long enough for solvolytic decomposition to compete effectively with metathesis.<sup>[5]</sup> This is exemplified by the self-metathesis (CM dimerisation) of alcohol **16** pro-



**Scheme 2.** CM in protic solvents catalysed by **3a**.

moted by **3a** in the presence of water, which proceeded with only modest conversion to yield **17** (Scheme 2).<sup>[14]</sup> In general we found that across a range of substrates, the promotion of conventional CM reactions under these conditions was beyond the capability of either **2** or **3a**. However, in methanol it was possible to quantitatively ring-open norbornene **18** in the presence of **3a** and allyltrimethylsilane to give **19** in a selective ring-opening cross-metathesis (ROM-CM) reaction (Scheme 2). To the best of our knowledge this represents the first example of an efficient and selective CM reaction in a protic solvent. In summary, it has been demonstrated that commercially available catalyst **2** is capable of effecting the homo- or heterogeneous RCM of previously challenging substrates in non-degassed DMF or methanol, respectively, in air. This catalyst possesses many advantages over current methanol-soluble systems<sup>[5a–f]</sup> in terms of superior activity/substrate scope, ready availability and ease of manipulation. The novel methanol-soluble catalyst **3a** can also be used effectively under these conditions, with the added advantage that it retains considerable metathesis activity in aqueous media (methanol-water and DMF-water mixtures), and has been shown to promote CM reactions in protic media. The application of these catalysts in the synthesis of biologically important molecules in aqueous solvent mixtures is currently being pursued.

## Experimental Section

### Synthesis of **3a**

A stirred mixture of **2** (200 mg, 0.235 mmol), 2,4-diisopropoxy-styrene (104 mg, 0.472 mmol) and CuCl (23.3 mg, 0.235 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) under nitrogen was heated at 45 °C for 1 h. After cooling, evaporation of the solvent and flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/hexane 1:1) of the residue gave **3a** as a green solid; yield: 135 mg (81%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 16.17 (s, 1H), 7.05 (s, 4H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.37 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.30 (s, 1H), 4.81 (septet, *J* = 6.1 Hz, 1H), 4.51 (septet, *J* = 6.1 Hz, 1H), 4.17 (s, 4H), 2.47 (bs, 12H), 2.39 (s,

6H), 1.28 (d, *J* = 6.1 Hz, 6H), 1.26 (d, *J* = 6.1 Hz, 6H); anal. calcd. for C<sub>34</sub>H<sub>44</sub>N<sub>2</sub>Cl<sub>2</sub>O<sub>2</sub>Ru (684.72): C 59.64, H 6.48, N 4.09%; found: C 59.34, H 6.85, N 3.51%.

### RCM General Procedure

A solution of the substrate (0.06 mmol) in solvent (1.2 mL) was added to the catalyst (0.003 mmol) in air and stirred at rt for 12 h. Ethyl vinyl ether (2 mL) was added, the solution evaporated to dryness under vacuum, and the residue analysed by <sup>1</sup>H NMR spectroscopy. Where DMF was used as solvent, MTBE (10 mL) and H<sub>2</sub>O (5 mL) were added after the ethyl vinyl ether addition. Separation of the layers and washing of the organic extracts with H<sub>2</sub>O (3 × 5 mL) gave a crude solution which could be dried (MgSO<sub>4</sub>), concentrated under vacuum and analysed by <sup>1</sup>H NMR.

## Acknowledgements

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## References and Notes

- [1] For reviews, see: a) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29; b) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; c) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; d) M. L. Randall, M. L. Snapper, *J. Mol. Cat. A* **1998**, *133*, 29–40; e) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2144; *Angew. Chem. Int. Ed.* **1997**, *36*, 2036–2056.
- [2] a) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110; b) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956.
- [3] Other active NHC-based catalysts: a) J. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678; b) L. Ackermann, A. Fürstner, T. Weskamp, F. J. Kohl, W. A. Herrmann, *Tetrahedron Lett.* **1999**, *40*, 4787–4790; c) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
- [4] For recent exceptions, see: a) J. Dowden, J. Savović, *Chem. Commun.* **2001**, 37–38; b) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955.
- [5] a) B. Mohr, D. M. Lynn, R. H. Grubbs, *Organometallics* **1996**, *15*, 4317–4325; b) D. M. Lynn, B. Mohr, L. M. Henling, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 6601–6609; c) D. M. Lynn, B. Mohr, R. H. Grubbs, *J. Am. Chem. Soc.* **1998**, *120*, 1627–1628; d) T. A. Kirkland, D. M. Lynn, R. H. Grubbs, *J. Org. Chem.* **1998**, *63*, 9904–9909; e) D. M. Lynn, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 3187–3193; f) T. Rölle, R. H. Grubbs, *Chem. Commun.* **2002**, 1070–1071.
- [6] a) S. Gessler, S. Randl, S. Blechert, *Synlett* **2001**, 430–433; b) J. Cossy, S. BouzBouz, A. H. Hoveyda, *J.*

- Organomet. Chem.* **2001**, 634, 216 – 221; c) S. Imhof, S. Randl, S. Blechert, *Chem. Commun.* **2001**, 1692 – 1693; d) S. BouzBouz, J. Cossy, *Org. Lett.* **2001**, 3, 1451 – 1454; d) S. Randl, S. J. Connon, S. Blechert, *Chem. Commun.* **2001**, 1796 – 1797.
- [7] S. J. Connon, S. Blechert, *Bioorg. Med. Chem. Lett.* **2002**, 12, 1873 – 1876.
- [8] a) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, 122, 8168 – 8179; b) S. Gessler, S. Randl, S. Blechert, *Tetrahedron Lett.* **2000**, 41, 9973 – 9976.
- [9] Pre-catalyst **2** is initially insoluble in MeOH, after 12 h a homogeneous solution is observed.
- [10] Catalyst **1a** is active under aqueous-emulsion conditions: D. M. Lynn, S. Kanaoka, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, 118, 784 – 790.
- [11] M. Ulman, R. H. Grubbs, *Organometallics* **1998**, 17, 2484 – 2489.
- [12] a) H. Wakamatsu, S. Blechert, *Angew. Chem.* **2002**, 114, 832 – 834; *Angew. Chem. Int. Ed.* **2002**, 41, 794 – 796; b) H. Wakamatsu, S. Blechert, *Angew. Chem.* **2002**, 114, 2509 – 2511; *Angew. Chem. Int. Ed.* **2002**, 41, 2403 – 2405; c) M. Zaja, S. Blechert, unpublished results.
- [13] It is noteworthy that **2** is partially soluble in DMF-H<sub>2</sub>O (3:1), this was the only solvent mixture in which **3a** did not outperform **2**.
- [14] In 100% methanol, the less stable catalyst **3b** has been previously reported to give a significantly higher conversion in this reaction (see ref.<sup>[7]</sup>). Since, in the present study we found **3b** to be inferior to **3a** in metathesis reactions involving protic solvents, the poor conversion observed in aqueous solvent would indicate that the presence of water (and not the potentially chelating allylic hydroxy group) is the main conversion-reducing factor in the CM dimerisation reaction involving **3a**.