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A simple and practical preparation of an efficient water soluble olefin metathesis catalyst†

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This study details homogeneous olefin metathesis in water catalysed by a di-ammonium functionalised Ru-alkylidene complex. A facile gram scale synthesis of an air stable catalyst precursor which can be readily converted to its water soluble derivative is described. The di-ammonium functionalised Ru-alkylidene complex facilitates a range of ring-closing metathesis (RCM) and cross-metathesis (CM) reactions in water.

Introduction

Ru-alkylidene catalysed olefin metathesis has become a powerful tool for the formation of new C–C double bonds.[1] The commercial availability of bench stable catalysts, generally mild reaction conditions employed and functional group tolerance of the catalysts have permitted wide-spread application of this chemistry into areas such as natural product synthesis,[2] materials science[3] and the pharmaceutical industry.[4] There is still considerable interest in improving the capabilities of Ru-based metathesis catalysts in the areas of *Z*-selectivity,[5] efficient ethenolysis,[6] and use of less expensive organometallic species.[7] Furthermore, with increasing demand for greener variants of existing chemistry,[8] as well as ongoing interest in accessing biologically relevant molecules, olefin metathesis in water is an area which calls for further research and development. Importantly, many polar ionic substrates (such as those presented in Table 1) have poor solubility in toluene or dichloromethane and therefore suffer from low reactivity in traditional organic media. Therefore, development of efficient aqueous phase olefin metathesis would provide a complimentary extension to the scope of this chemistry.

Numerous strategies have been developed to facilitate olefin metathesis reactions in aqueous media including using solvent mixtures,[9] additives,[10] on water metathesis[11] and catalyst modification.[12] In addition, several heterogeneous catalysts capable of functioning in water have been reported in water. Whilst examples of tailored Ru-alkylidene catalysts (**1–5**) (Fig. 1) for olefin metathesis in water have been reported,[13] some vital limitations in this area of research still remain. In particular, Ru-complexes **2**, **4** and **5** possess water solubilising functionalities on the benzylidene ligand.[14] Upon dissociation of this labile ligand, the propagating Ru-alkylidene species must operate independent of the initially appended water solubilising functionality. On the other hand, functionalising the non-dissociating NHC ligand with hydrophilic groups is a promising tactic to maintain homogeneity of the active propagating catalyst in water throughout the entire reaction cycle.[15]

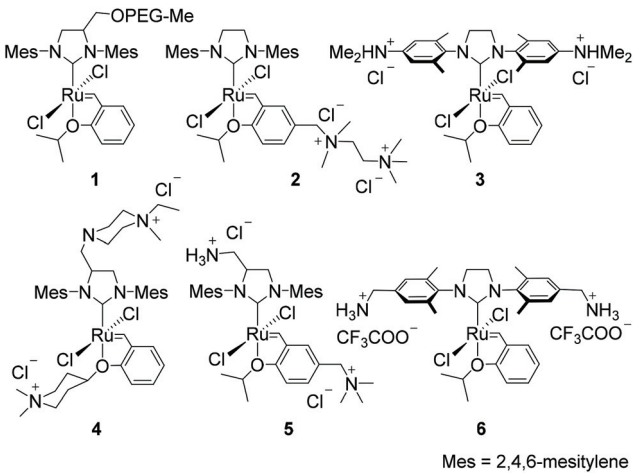

Fig. 1 Water soluble Ru-alkylidene catalysts.

However, efforts towards this end have been met with limited success in terms of catalyst activity and practicality. For example, Schanz and coworkers[16] demonstrated the potential utility of ammonium functionalities on the NHC ligand to solubilise the Ru-alkylidene complex **3** in water. However, relatively low metathesis activity was reported for **3**, possibly due to the electron withdrawing effects of the ammonium groups directly attached to the aryl systems.[17] Grubbs and coworkers[18] reported the polyethylene glycol based complex **1** with higher catalytic activity in metathesis reactions. The synthesis of this

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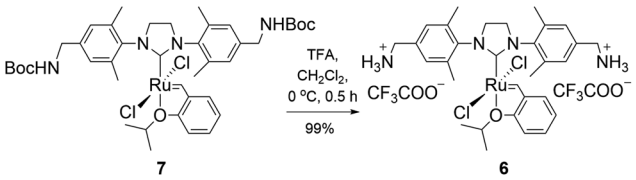
complex however required the manipulation and purification of polymeric intermediates. In our ongoing efforts to expand the utility of Ru-alkylidene catalysed olefin metathesis chemistry[19] we sought a simple, active and easily accessible Ru-alkylidene catalyst which operates homogeneously in water.

Results and discussion

Herein we report the preparation of an *in situ* generated Ru-alkylidene catalyst **6** (Fig. 1), from bench-stable precursor **7**, and examine its catalytic activity in ring-closing metathesis (RCM) and cross-metathesis (CM) reactions performed in water. Complex **7** was prepared in six steps from the benzonitrile **8**[20] (Scheme 1). Reduction of **8** with $LiAlH_4$, followed by treatment with Boc anhydride afforded carbamate **9**. Condensation of **9** with glyoxal and subsequent reduction with $NaBH_4$ gave diamine **10**. Treatment of **10** with triethyl orthoformate in the presence of NH_4BF_4 gave imidazolinium salt **11**. It is noteworthy that the preparation of imidazolinium salt **11** from the starting benzonitrile **8** required only one chromatographic purification (of the diamine **10**) and consequently enabled access to **11** in a highly scalable (>10 g batch) fashion. Deprotonation of carbene precursor **11** using KHMDS or KO^{t}Bu followed by reaction with **HGI** provided the Ru-alkylidene complex **7**, however in low yields. Deleterious deprotonation of the acidic NH protons of the carbamate groups was deemed responsible for the low yield and unwanted by–products. Importantly, Taton and coworkers[21] recently reported the use of imidazolinium hydrogen carbonate salts as an alternative source of carbenes without the need for strong base. We applied this approach to our synthetic route by first converting the tetrafluoroborate salt **11** to the bicarbonate salt **12** using an ion exchange resin.[22] The bicarbonate salt **12** was subsequently treated with **HGI** at 80 °C in toluene to afford the desired Ru–alkylidene **7** in good yield. Complex **7** was easily isolated and no storage precautions were necessary for this air stable, non-hygroscopic complex.

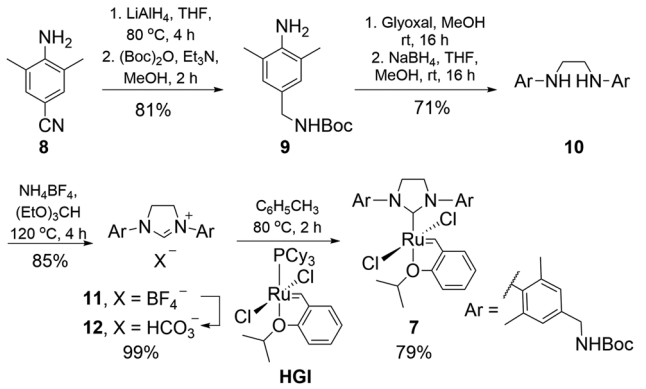
Application of catalyst precursor **7** to olefin metathesis reactions in water was investigated. Acid cleavage of the Boc groups with trifluoroacetic acid (TFA) in CH_2Cl_2 followed by removal of volatiles under reduced pressure generated the di-ammonium complex **6** as a green solid (Scheme 2). Subsequent dissolution of **6** in water at room temperature was facile; 5 mg of **6** readily dissolves in 1 ml of D_2O giving a molar solution (0.005 mM) comparable to that employed in reactions involving organic solvents. Conveniently, the generation of **6** (from complex **7**) and the subsequent olefin metathesis reaction in water could be performed in a one-pot procedure, without the need for purification of **6**.



Scheme 2 Activation of catalyst precursor **7** to afford the water soluble di-ammonium complex **6**.

The olefin metathesis activity of complex **6** was investigated with a model RCM reaction in D_2O (Fig. 2). The rate of RCM of diene **13** at various temperatures was followed by ^{1}H-NMR spectroscopy. At room temperature, the reaction reached equilibrium after 1 h with an 87% conversion to the ring-closed product **14**. At 50 °C, the reaction proceeded to completion after 40 minutes. Remarkably, catalyst **6** showed high activity at 80 °C with complete conversion of diene **13** to the cyclised product **14** in 10 minutes.

The turnover number (TON) of **6** was also studied (Table 1, entry 1). At a loading of 0.1 mol% of catalyst **6**, RCM of diene **15** proceeded to 91% conversion, equating to a TON of greater than 900. Using 5 mol% of **6** gave optimal metathesis results and these conditions were used for subsequent reactions (Table 1). The RCM of dienes **13**, **15** and **16** gave complete conversion to cyclised products **14**, **17** and **18** respectively (entries 1–3). Of particular interest to our ongoing studies towards marine alkaloids,[23] RCM of **19** gave the 1-azaspirocycle **20** (entry 4). RCM of dienes **21**, **22** and **23** gave the pyrrolidinium structures **24**, **25** and **26** respectively in moderate conversions



Scheme 1 Synthesis of Ru-alkylidene catalyst precursor **7**.

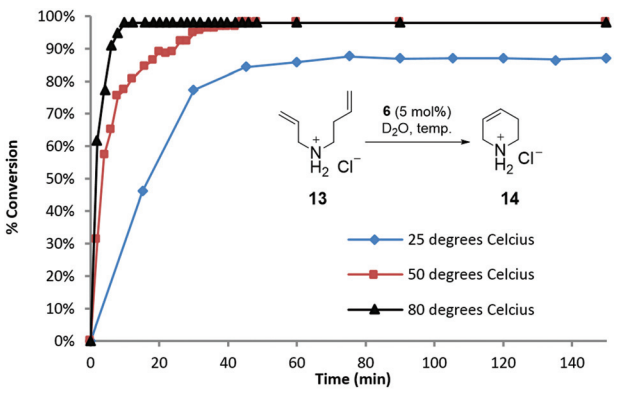


Fig. 2 RCM activity of **6** at various temperatures.

Table 1 Olefin metathesis reactions catalysed by **6** in D_2O[a]

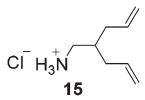
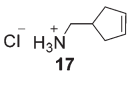
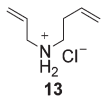
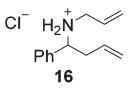
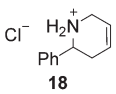
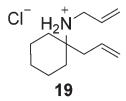
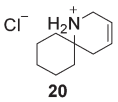
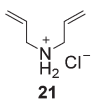
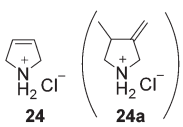
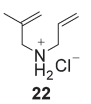
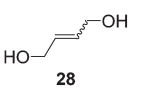
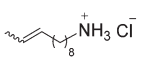
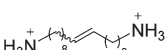
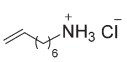
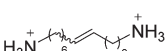
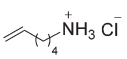
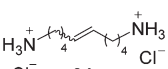
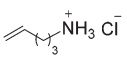
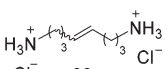
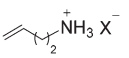
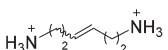
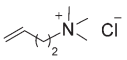
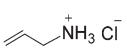
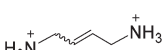
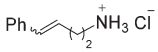
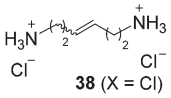
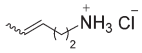
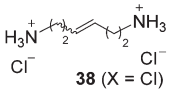
Entry	Substrate	Product	Conversion
1	 **15**	 **17**	91%[b] 95%[c]
2	 **13**	 **14**	>95% 88%[c]
3	 **16**	 **18**	>95% 94%[c]
4	 **19**	 **20**	56%
5	 **21**	 **24** **24a**	61% (29%)
6	 **22**	 **25**	47%
7	 **23**	 **26**	25%
8	 **27**	 **28**	>95%
9	 **29**	 **30**	>95%
10	 **31**	 **32**	>95% 92%[c]
11	 **33**	 **34**	>95% 90%[c]
12	 **35**	 **36**	0%
13	 **37** X = Cl, BF_4, OTf, SO_4^{2-}	 **38**	0%
14	 **39**	 **40**	0%
15	 **41**	 **42**	0%

Table 1 *(Contd.)*

Entry	Substrate	Product	Conversion
16	 **43**	 **38** (X = Cl)	0%
17	 **44**	 **38** (X = Cl)	33%

[a] Metathesis reactions were performed using 5 mol% **6** in D_2O at 80 °C for 1 h. The initial substrate concentration was 0.1 M in D_2O. Conversions were determined by ^{1}H-NMR spectroscopy. [b] Reaction performed using 0.1 mol% precatalyst **6**. [c] Isolated yield.

(entries 5–7). Isolation of selected examples was achieved *via* simple aqueous extraction to afford pure ammonium products (see Table 1 and Experimental section).

Studies on CM in water began with the homo–coupling of allyl alcohol (**27**) to give diol **28** in excellent conversion (entry 8). Self CM of long alkenylammonium salts both with a non-terminal alkene (**29**) and a terminal methylene group (**31**) gave almost quantitative conversion to the di-ammonium salts **30** and **32** respectively (entries 9 and 10). Similarly, the hexenylammonium salt **33** gave excellent conversion to the cross-product **34** (entry 11). To the best of our knowledge, this is the first report of CM of amine salts in aqueous systems.

Unexpectedly, short chain alkenylammonium salts were poor substrates for CM in water. It was important to assess these substrates because of their immediate utility in polyamide synthesis. The attempted self CM of the pentenylammonium chloride **35**, butenylammonium chloride **37** (X = Cl), trimethylammonium analogue **39** and allylammonium chloride **41** all failed to afford their respective cross–products (entries 12–15). We have previously reported that CM of the butenylammonium salt **37** in dichloromethane was dependent on the nature of the anion. In this previous report, a low yield was obtained for the CM of the chloride salt **37** (X = Cl) in dichloromethane (38%) but a satisfactory conversion of the tetrafluoroborate salt **37** ($X = BF_4$) was observed (91%).[24] Unfortunately, in aqueous systems, the sulfate, tetrafluoroborate and triflate salts were also unreactive (entry 13).

From our studies, two factors seem to play important roles in CM reactions catalysed by **6** in water on substrates containing ammonium functionality. Firstly, the length of the linker between the alkene and the ammonium groups has a dramatic impact on the reactivity of the substrate. Substrates containing linkers shorter than three carbons (such as **35**, **37** and **41**) have no reactivity, possibly due to formation of a non-productive Ru-nitrogen chelate **45** (Fig. 3). Evidence for decomposition of related catalyst systems has recently been reported.[25] Whilst short chain substrates have been shown to be reactive in organic solvents (as mentioned above) we postulate that in water, an equilibrium between the ammonium group and its corresponding free amine may allow the Lewis basic nitrogen

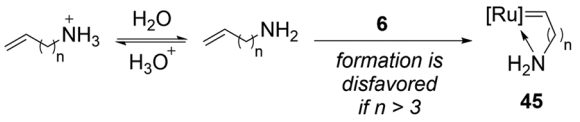


Fig. 3 Proposed catalyst deactivation pathway for alkenylammonium substrates.

to coordinate to the Ru-centre and cause catalyst deactivation.[26] Curiously, however, analogous amine motifs are also present in RCM substrates **13**, **15** and **16**, yet metathesis yields for these substrates is near quantitative. We currently unable to explain the difference in reactivity observed in our RCM and CM reactions but offer the following explanation: In the RCM reactions, where the second olefin is tethered, the rate of RCM exceeds the rate of catalyst deactivation. In the case of the CM reactions, charge repulsion between the positively-charged Ru-alkylidine and the second ammonium alkene could disfavour coordination and/or formation of a productive metallocyclobutane. In comparison, substrates containing a longer linker (such as **29**, **31** and **33**), where the pendant ammonium motif is removed from the coordination sphere, may not suffer from this effect and thus showed exceptional CM reactivity in water.

Secondly, our results also suggest that deactivation of catalyst **6** may also be occurring *via* the Ru-methylidene intermediate **46** (Fig. 4).[27] This is evident by comparing the attempted CM of **37** (X = Cl) (entry 13) which gave no desired cross-product, with the CM of **44** (entry 17) which gave 33% conversion to **38**. Whilst both **37** and **44** can give the same cross-product (**38**) the difference in the two substrates is that the terminal alkene **37** must turnover *via* a less stable Ru-methylidene intermediate **46** whilst the non-terminal "equivalent" **44** turns over *via* a more stable Ru-ethylidene intermediate **47**. Cycling *via* more stable catalyst intermediates may explain the formation of product from substrate **41**, albeit in a very modest yield. In order to further investigate non-terminal olefin substrates, the styrenyl analogue **43** was also attempted, however no reaction was observed (entry 16). This study suggests that careful consideration of Ru–alkylidene intermediates may assist in these challenging CM reactions in aqueous solvents. Despite the challenges experienced during CM of the short chain alkenylammonium salts in water, catalyst **6** is clearly able to facilitate high yielding CM and RCM reactions in water.

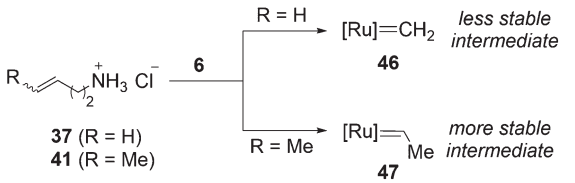
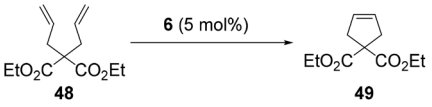


Fig. 4 Terminal and internal alkene substrates cycle *via* different Ru-alkylidene intermediates during CM reaction.

Table 2 RCM of **48** catalysed by **6** in organic solvent/water mixtures



Entry	Solvent system	Temp. (°C)	Time (h)	Conversion[a] (%)
1	EtOAc/H_2O (1 : 1)	25	2	0
2	Toluene/H_2O (1 : 1)	25	2	0
3	CH_2Cl_2/H_2O (1 : 1)	25	2	6
4	THF/H_2O (1 : 1)	25	2	31
5	THF/H_2O (1 : 1)	40	2	>95
6	THF/H_2O (1 : 1)	40	2	75[b]

[a] Reactions were conducted using **6** (5 mol%) for 2 h. Conversions were determined by ^{1}H-NMR spectroscopy. [b] Reaction with catalyst recycled from entry 5.

Although the primary focus of this work was to perform metathesis reactions on polar substrates in pure water, the use of a mixed solvent system opened up a tantalising opportunity to extend the chemistry and recycle the catalyst *via* simple extractive separation. Towards this end, metathesis of diethyl diallylmalonate **48** in biphasic solvent systems was investigated (Table 2). Solvent mixtures of EtOAc/H_2O (entry 1) and toluene/H_2O (entry 2), both gave no reaction, and a CH_2Cl_2/H_2O mixture facilitated only trace conversion to the ring-closed product **49** (entry 3). A promising result was obtained using aqueous THF which gave 31% conversion to product **49** (entry 4). When the reaction was heated to 40 °C for two hours, excellent (>95%) conversion to **49** was observed (entry 5). At the completion of this reaction, the catalyst was removed *via* simple phase separation and re-exposed to a fresh sample of diester **48** (Table 2, entry 6). This resulted in only moderate conversion to **49** (75%) suggesting inefficient recapture of the Ru-alkylidene or decomposition of the catalyst.

Conclusion

In summary, a simple and highly active water soluble olefin metathesis catalyst (**6**) has been developed. The catalyst preparation is facile and highly scalable. The complex can be stored as a stable and non-hydroscopic precatalyst (**7**) and conveniently activated *in situ* to perform a range of CM and RCM reactions in water. Importantly, the catalyst displays exceptional RCM and CM activity on challenging polar substrates which are also highly *insoluble* in organic solvents without derivatisation. It should be highlighted that this work presents the first examples of CM of amine salts in pure water.

Experimental

Dichloromethane (CH_2Cl_2) was supplied by Merck and distilled over CaH_2 prior to use. Diethyl ether (Et_2O), tetrahydro-

furan (THF) and toluene ($C_6H_5CH_3$) were supplied by Merck and distilled over potassium prior to use. Acetic acid (AcOH), ethyl acetate (EtOAc), hexane, methanol (CH_3OH) and triethylamine (Et_3N) were used as supplied by Merck. 4-Bromo-2,6-dimethylaniline, cuprous cyanide (CuCN), lithium aluminum hydride ($LiAlH_4$), di-*tert*-butyl dicarbonate ($(Boc)_2O$), glyoxal solution 40 wt% in H_2O, sodium borohydride ($NaBH_4$), ammonium tetrafluoroborate (NH_4BF_4), triethyl orthoformate ($(EtO)_3CH$), ammonium bicarbonate (NH_4HCO_3) and dichloro(*o*-isopropoxyphenylmethylene)(tricyclohexylphosphine)ruthenium(II) (**HGI**) were used as supplied by Sigma-Aldrich. D_2O was purchased from Cambridge Isotopes Laboratory and degassed by bubbling with argon (30 minutes).

4-Amino-3,5-dimethylbenzonitrile 8

Compound **8** was prepared following a modified procedure developed by Gerritz and coworkers.[28] A magnetically stirred solution of 4-bromo-2,6-dimethylaniline (30.0 g, 150 mmol) and CuCN (26.7 g, 300 mmol) in NMP (400 mL) was heated to 160 °C for 16 h. After cooling to room temperature, water (150 mL) and ammonium hydroxide (150 mL) were added and the mixture stirred for a further 0.5 h. During this period, a grey precipitate formed, and the mixture was filtered. The filtrate was extracted with EtOAc (3 × 200 mL) and the combined organic extracts washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **7** (18.2 g, 83%) as a colourless solid, m.p. 106.0–107.5 °C. IR ν_{max} 3476m, 3384m, 2205s, 1631s, 1599s, 1487s, 1431s, 1323s cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 2H), 4.16 (br s, 2H), 2.17 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.0, 132.2, 121.8, 120.6, 99.8, 17.4. All data was consistent with that previously reported.[23]

tert-Butyl(4-amino-3,5-dimethylbenzyl)carbamate 9

A solution of benzonitrile **8** (17.5 g, 120 mmol) in THF (100 mL) was added dropwise to a magnetically stirred suspension of $LiAlH_4$ (9.31 g, 245 mmol) in THF (500 mL). The mixture was stirred under reflux for 4 h then cooled to room temperature. The reaction was quenched by careful addition of H_2O (5 mL) and 1 M NaOH (5 mL) and stirred for 0.5 h. The mixture was dried (Na_2SO_4), filtered and the filtrate concentrated under reduced pressure to afford the amine as a clear colourless oil. To this residue was added CH_3OH (250 mL) and Et_3N (25 mL). The mixture was cooled to 0 °C and a solution of $(Boc)_2O$ (26.2 g, 120 mmol) in CH_3OH (40 mL) was added over 2 minutes. The reaction was stirred for 2 h at room temperature. The mixture was diluted with Et_2O (200 mL) and washed with H_2O (2 × 150 mL) followed by brine (200 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **9** (24.3 g, 81%) as a colourless solid, m.p. 100.2–101.3 °C, which was used without further purification. IR ν_{max} 3383m, 3347m, 2927m, 1673s, 1622m, 1515s, 1490s, 1155s cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 2H), 4.76 (br s, 1H), 4.15 (d, J = 5.2 Hz, 2H), 3.57 (br s, 2H), 2.16 (s, 6H), 1.46 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.9, 142.1, 128.1, 127.9, 121.9, 79.2, 44.5, 28.5, 17.6. HRMS (ESI^+, MeOH): m/z 251.1749 $[M + H]^+$, $C_{14}H_{23}N_2O_2^+$ requires 251.1754.

Di-*tert*-butyl(((ethane-1,2-diylbis(azanediyl))bis(3,5-dimethyl-4,1-phenylene))bis(methylene))dicarbamate 10

The intermediate diimine was prepared following a modified procedure of Hintermann.[29] A solution of glyoxal (5.80 g, 40 wt% in H_2O, 40 mmol) and acetic acid (0.1 mL) was added to a magnetically stirred solution of carbamate **9** (20 g, 79.9 mmol) in CH_3OH (50 mL) at 50 °C. The mixture was stirred at room temperature for 16 h. The product precipitated from the solution and the suspension was filtered. The resultant yellow solid was washed with CH_3OH (2 × 15 mL) and dried to constant weight under reduced pressure to afford the pure diimine. The filtrate was concentrated under reduced pressure to a volume of 30 mL and set aside for a second crystallisation. Total yield of diimine: 15.7 g (75%) as a yellow solid, m.p. 185.9–187.5 °C. IR ν_{max} 3339 m, 2973m, 2932m, 1708s, 1519m, 1246m, 1158s, 1124m cm^{-1}. ^{1}H–NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 2H), 7.00 (s, 4H), 4.86 (br s, 2H), 4.24 (d, J = 7.6 Hz, 4H), 2.16 (s, 12H), 1.47 (s, 18H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 163.6, 156.0, 149.1, 135.4, 127.6, 126.9, 79.6, 44.4, 28.6, 18.4. HRMS (ESI^+, MeOH): m/z 523.3286 $[M + H]^+$, $C_{30}H_{43}N_4O_4^+$ requires 523.3279.

Reduction of the diimine was performed following a modified procedure of Nolan and coworkers.[30] $NaBH_4$ (6.54 g, 172 mmol) was carefully added to a magnetically stirred solution of the above diimine (15.0 g, 28.7 mmol) in THF (100 mL) and CH_3OH (50 mL) at 0 °C. The mixture was stirred at room temperature for 16 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (20 mL). The product was extracted with Et_2O (3 × 50 mL) and the combined organic extracts washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (1 : 1, EtOAc : hexane) to afford **10** (14.4 g, 95%) as a colourless solid, m.p. 107.8–108.7 °C. IR ν_{max} 3339m, 3230m, 2969m, 1687s, 1538m, 1480m, 1271m, 1250m, 1155m, 1133m cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.92 (s, 4H), 4.81 (br s, 2H), 4.18 (d, J = 5.2 Hz, 4H), 3.35 (br s, 2H), 3.19 (s, 4H), 2.29 (s, 12H), 1.47 (s, 18H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.0, 144.9, 132.6, 129.9, 128.3, 79.4, 49.0, 44.4, 28.5, 18.7. HRMS (ESI^+, MeOH): m/z 527.3596 $[M + H]^+$, $C_{30}H_{47}N_4O_4^+$ requires 527.3592.

1,3-Bis(4-(((*tert*-butoxycarbonyl)amino)methyl)-2,6-dimethylphenyl)-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate 11

NH_4BF_4 (2.48 g, 23.7 mmol) was added to a solution of diamine **10** (12.5 g, 23.7 mmol) in $(EtO)_3CH$ (35 mL). The mixture was stirred at 120 °C for 16 h. The reaction was cooled to room temperature and the product precipitated from solution. The mixture was filtered and the solid was washed with CH_2Cl_2 (10 mL) and Et_2O (10 mL) and dried under reduced pressure to afford imidazolinium salt **11** (12.6 g, 85%) as a colourless solid, m.p. 240.3 °C (decomp.). IR ν_{max} 3333m, 2976m, 1690s, 1637s, 1260s, 1169m, 1046s cm^{-1}. ^{1}H-NMR

(400 MHz, CD_3OD): δ 8.87 (s, 1H), 7.18 (s, 4H), 4.53 (s, 4H), 4.20 (s, 4H), 2.43 (s, 12H), 1.45 (s, 18H). ^{13}C-NMR (100 MHz, CD_3OD): δ 162.1, 158.4, 143.9, 137.0, 133.1, 129.1, 80.5, 52.6, 44.6, 28.8, 17.8. ^{19}F-NMR (282 MHz, CD_3OD): δ −154.7. HRMS (ESI^+, MeOH): m/z 537.3449 $[M + H]^+$, $C_{31}H_{45}N_4O_4^+$ requires 537.3435.

Ru-alkylidene complex 7

A glass column (2 cm diameter) packed with 5.0 g of Amberlite resin IRA-400 (Cl^-) was washed with H_2O (30 mL). A solution of sat. NH_4HCO_3(aq) (50 mL) was passed slowly through the resin. The resin was washed with H_2O (30 mL) followed by H_2O/CH_3OH mixture (1 : 1) (30 mL) then finally CH_3OH (30 mL). A solution of imidazolinium BF_4 salt **11** (1.29 g, 2.07 mmol) dissolved in minimal CH_3OH (15 mL) was loaded onto the resin, and eluted with CH_3OH (25 mL). The combined eluent was concentrated and rigourlessly dried under reduced pressure to afford imidazolinium HCO_3 salt **12** (1.22 g, 99%) as a colourless solid. To the vessel containing **12** (1.22 g, 2.04 mmol) was added **HGI** (919 mg, 1.53 mmol) and a stir bar. The vessel was evacuated and backfilled with N_2 (three times). Toluene (30 mL) was added to the vessel *via* syringe and the mixture was stirred at 80 °C for 2 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica column chromatography (1 : 1 Et_2O : hexane → 20 : 1 Et_2O : hexane) (green band was collected) to afford Ru-alkylidene **7** (1.04 g, 79%) as a green solid, m.p. 158.1 °C (decomp.). IR ν_{max} 3361m, 2971m, 1697s, 1515m, 1482m, 1365m, 1259s, 1165s cm^{-1}. ^{1}H–NMR (400 MHz, C_6D_6): δ 16.6 (s, 1H), 7.24 (d, J = 6.4 Hz, 1H), 7.11 (t, J = 6.4 Hz, 1H), 6.96 (s, 4H), 6.79 (t, J = 6.4 Hz, 1H), 6.31 (d, J = 6.4 Hz, 1H), 4.52 (br s, 2H), 4.51 (sept, J = 5.2 Hz, 1H), 4.23 (d, J = 4.4 Hz, 4H), 3.37 (s, 4H), 2.50 (s, 12H), 1.50 (s, 18H), 1.31 (d, J = 5.2 Hz, 6H). ^{13}C-NMR (100 MHz, C_6D_6): δ 292.5, 213.1, 155.9, 152.7, 145.9, 140.4, 139.9, 129.1, 128.2, 127.9, 122.7, 122.4, 113.2, 79.0, 75.2, 51.2, 44.5, 30.2, 28.6, 21.4. HRMS (ESI^+, MeOH): m/z 857.3165 $[M + H]^+$, $C_{41}H_{57}Cl_2N_4O_5{}^{102}Ru^+$ requires 857.2744. Elemental analysis found: C, 56.6; H, 6.8; N, 6.3. $C_{41}H_{56}Cl_2N_4O_5Ru$ requires C, 57.5; H, 6.6; N, 6.5% $C_{41}H_{56}Cl_2N_4O_5Ru + H_2O$ requires C, 56.3; H, 6.7; N, 6.4%.

General procedure for olefin metathesis in water

Trifluoroacetic acid (0.50 mL) was added dropwise to a stirred solution of **7** (10.0 mg, 0.012 mmol, 5 mol%) in CH_2Cl_2 (1.0 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then concentrated under reduced pressure to afford **6** as a green solid. Fresh CH_2Cl_2 (2.0 mL) was added to the solid and the resultant suspension was concentrated under reduced pressure to remove remaining traces of trifluoroacetic acid. The complex **6** was dried under reduced pressure and a solution of the substrate (0.23 mmol) in D_2O (2.3 mL) was added. The homogeneous mixture was stirred at 80 °C for 1 h. The reaction mixture was analysed by ^{1}H-NMR spectroscopy. Isolation of metathesis products was performed on selected substrates. For isolation, the reaction mixture was cooled to r.t. and diluted with H_2O (5 mL). The aqueous phase was washed with Et_2O (5 mL) and the organic phase discarded. The aqueous phase was basified with 1 M NaOH solution (2 mL) and the free amine extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and to the filtrate was added a saturated solution of HCl in Et_2O (2 mL). The resultant cloudy suspension was then concentrated *in vacuo* to afford the corresponding ammonium hydrochloride salt. For compound characterisation see ESI.†

Representative procedure for olefin metathesis in water/solvent mixtures

A solution of **6** in H_2O was prepared as described in the General Procedure above. A solution of **48** (0.24 mmol, 58 mg) in THF (2.3 mL) was added to the aqueous solution of **6**. The reaction mixture was heated to 40 °C for 2 hours. After cooling to room temperature, hexane (3 mL) was added to the reaction mixture. The organic layer was removed from the reaction *via* syringe, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was analysed by ^{1}H-NMR spectroscopy. Catalyst recycling experiments involved introduction of a fresh batch of **48** (0.24 mmol, 58 mg) in THF (2.3 mL) to the aqueous solution and repeating the above procedure.

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Notes and references

1 (*a*) A. H. Hoveyda and A. R. Zhugralin, *Nature*, 2007, **450**, 243–251; (*b*) G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746–1787.
2 (*a*) A. V. Statsuk, D. Liu and S. A. Kozmin, *J. Am. Chem. Soc.*, 2004, **126**, 9546–9547; (*b*) D. G. Gillingham and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2007, **46**, 3860–3864.
3 (*a*) J. C. Mol, *J. Mol. Catal. A: Chem.*, 2004, **213**, 39–45; (*b*) S. R. White, N. R. Sottos, P. H. Geubelle, J. S. Moore, M. R. Kessler, S. R. Sriram, E. N. Brown and S. Viswanathan, *Nature*, 2001, **409**, 794–797.
4 (*a*) T. Nicola, M. Brenner, K. Donsbach and P. Kreye, *Org. Process Res. Dev.*, 2005, **9**, 513–515; (*b*) N. K. Yee, V. Farina, I. N. Houpis, N. Haddad, R. P. Frutos, F. Gallou, X.-J. Wang, X. Wei, R. D. Simpson, X. Feng, V. Fuchs, Y. Xu, J. Tan, L. Zhang, J. Xu, L. L. Smith-Keenan, J. Vitous, M. D. Ridges, E. M. Spinelli and M. Johnson, *J. Org. Chem.*, 2006, **71**, 7133–7145.
5 (*a*) K. Endo and R. H. Grubbs, *J. Am. Chem. Soc.*, 2011, **133**, 8525–8527; (*b*) B. K. Keitz, K. Endo, P. R. Patel, M. B. Herbert and R. H. Grubbs, *J. Am. Chem. Soc.*, 2012, **134**, 693–699; (*c*) G. Occhipinti, F. R. Hansen, K. W. Tornroos and V. R. Jensen, *J. Am. Chem. Soc.*, 2013,

135, 3331–3334; (*d*) L. E. Rosebrugh, M. B. Herbert, V. M. Marx, B. K. Keitz and R. H. Grubbs, *J. Am. Chem. Soc.*, 2013, **135**, 1276–1279; (*e*) R. K. M. Khan, S. Torker and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2013, **135**, 10258–10261; (*f*) M. J. Koh, R. K. M. Khan, S. Torker, M. Yu, M. S. Mikus and A. H. Hoveyda, *Nature*, 2015, **517**, 181–186.

6 (*a*) R. M. Thomas, B. K. Keitz, T. M. Champagne and R. H. Grubbs, *J. Am. Chem. Soc.*, 2011, **133**, 7490–7496; (*b*) V. M. Marx, A. H. Sullivan, M. Melaimi, S. C. Virgil, B. K. Keitz, D. S. Weinberger, G. Bertrand and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2015, **54**, 1919–1923.

7 (*a*) G. Dazinger and K. Kirchner, *Organometallics*, 2004, **23**, 6281–6287; (*b*) A. Poater, E. Pump, S. V. C. Vummaleti and L. Cavallo, *Chem. Phys. Lett.*, 2014, **610–611**, 29–32; (*c*) M. Vasiliu, A. J. Arduengo and D. A. Dixon, *J. Phys. Chem. C*, 2014, **118**, 13563–13577; (*d*) S. Lwin, C. Keturakis, J. Handzlik, P. Sautet, Y. Li, A. I. Frenkel and I. E. Wachs, *ACS Catal.*, 2015, **5**, 1432–1444.

8 (*a*) G. Szczepaniak, K. Kosiński and K. Grela, *Green Chem.*, 2014, **16**, 4474–4492; (*b*) P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301–312.

9 (*a*) S. J. Connon and S. Blechert, *Bioorg. Med. Chem. Lett.*, 2007, **12**, 1873–1876; (*b*) J. B. Binder, J. J. Blank and R. T. Raines, *Org. Lett.*, 2007, **9**, 4885–4888.

10 (*a*) B. H. Lipshutz, G. T. Aguinaldo, S. Ghorai and K. Voigtritter, *Org. Lett.*, 2008, **7–8**, 953–956; (*b*) B. H. Lipshutz and S. Ghorai, *Org. Lett.*, 2009, **11**, 705–708; (*c*) T. Matsuo, T. Yoshida, A. Fujii, K. Kawahara and S. Hirota, *Organometallics*, 2013, **32**, 5313–5319.

11 (*a*) L. Gulajski, P. Śledź, A. Lupa and K. Grela, *Green Chem.*, 2008, **10**, 279–282; (*b*) K. J. Davis and D. Sinou, *J. Mol. Catal. A: Chem.*, 2002, **177**, 173–178; (*c*) V. Polshettiwar and R. S. Varma, *J. Org. Chem.*, 2008, **73**, 7417–7419.

12 (*a*) A. Michrowska, L. Gulajski, Z. Karczmarska, K. Mennecke, A. Kirschning and K. Grela, *Green Chem.*, 2006, **8**, 685–688; (*b*) L. Gulajski, A. Michrowska, J. Naroznik, Z. Karczmarska, L. Rupnicki and K. Grela, *ChemSusChem*, 2008, **1**, 103–109; (*c*) D. Rix, H. Clavier, Y. Coutard, L. Gulajski, K. Grela and M. J. Mauduit, *Organomet. Chem.*, 2006, **691**, 5397–5405; (*d*) D. Rix, F. Caïjo, I. Laurent, L. Gulajski, K. Grela and M. Mauduit, *Chem. Commun.*, 2007, 3771–3773; (*e*) J. Pastva, K. Skowerski, S. J. Czarnocki, N. Žilková, J. Čejka, Z. Bastl and H. Balcar, *ACS Catal.*, 2014, **4**, 3227–3236; (*f*) A. Hryniewicka, I. Misztalewska, D. Czajkowska-Szczykowska, Z. Urbańczyk-Lipkowska, J. W. Morzycki and S. Witkowski, *Tetrahedron*, 2014, **70**, 6810–6816; (*g*) B. Ö. Öztürk, B. Sariaslan, N. P. Bayramgil and S. K. Şehitoğlu, *Appl. Catal., A*, 2014, **483**, 19–24.

13 (*a*) D. Burtscher and K. Grela, *Angew. Chem., Int. Ed.*, 2009, **48**, 442–454; (*b*) J. Tomasek and J. Schatz, *Green Chem.*, 2013, **15**, 2317–2338; (*c*) B. H. Lipshutz and S. Ghorai, Olefin Metathesis in Water and Aqueous Media, in *Olefin Metathesis: Theory and Practice*, ed. K. Grela, John Wiley & Sons, Inc., Hoboken, USA, 2014, pp. 515–521.

14 (*a*) J. P. Jordan and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2007, **46**, 5152–5155; (*b*) K. Skowerski, G. Szczepaniak, C. Wierzbicka, L. Gulajski, M. Bieniek and K. Grela, *Catal. Sci. Technol.*, 2012, **2**, 2424–2427.

15 C. Samojlowicz, M. Bieniek and K. Grela, *Chem. Rev.*, 2009, **109**, 3708–3742.

16 (*a*) S. L. Balof, S. J. P'Pool, N. J. Berger, E. J. Valente, A. M. Shiller and H.-J. Schanz, *Dalton Trans.*, 2008, 5791–5799; (*b*) J. Cabrera, R. Padilla, M. Bru, R. Lindner, T. Kageyama, K. Wilckens, S. L. Balof, H.-J. Schanz, R. Dehn, J. H. Teles, S. Deuerlein, K. Müller, F. Rominger and M. Limbach, *Chem. – Eur. J.*, 2012, **18**, 14717–14724.

17 (*a*) C. Luján and S. P. J. Nolan, *Organomet. Chem.*, 2011, **696**, 3935–3938; (*b*) E. Pump, A. Poater, M. Zirngast, A. Torvisco, R. Fischer, L. Cavallo and C. Slugovc, *Organometallics*, 2014, **33**, 2806–2813; (*c*) S. Manzini, C. A. Urbina-Blanco, D. J. Nelson, A. Poater, T. Lebl, S. Meiries, A. M. Z. Slawin, L. Falivene, L. Cavallo and S. P. Nolan, *J. Organomet. Chem.*, 2015, **780**, 43–48.

18 S. H. Hong and R. H. Grubbs, *J. Am. Chem. Soc.*, 2006, **128**, 3508–3509.

19 Z. J. Wang, W. R. Jackson and A. J. Robinson, *Org. Lett.*, 2013, **15**, 3006–3009.

20 Prepared from 2,6-dimethylaniline, see ESI.†

21 M. Fèvre, J. Pinaud, A. Leteneur, Y. Gnanou, J. Vignolle, D. Taton, K. Miqueu and J.-M. Sotiropoulos, *J. Am. Chem. Soc.*, 2012, **134**, 6776–6784.

22 E. Alcalde, I. Dinarès, A. Ibáñez and N. Mesquida, *Molecules*, 2012, **17**, 4007–4027.

23 Z. J. Wang, N. S. Spiccia, C. J. Gartshore, J. Illesinghe, W. R. Jackson and A. J. Robinson, *Synthesis*, 2013, 3118–3124.

24 C. P. Woodward, N. D. Spiccia, W. R. Jackson and A. J. Robinson, *Chem. Commun.*, 2011, **47**, 779–781.

25 (*a*) J. A. M. Lummiss, B. J. Ireland, J. M. Sommers and D. E. Fogg, *ChemCatChem*, 2014, **6**, 459–463; (*b*) S. Manzini, J. A. Fernández-Salas and S. P. Nolan, *Acc. Chem. Res.*, 2014, **47**, 3089–3101; (*c*) S. Manzini, D. J. Nelson, T. Lebl, A. Poater, L. Cavallo, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.*, 2014, **50**, 2205–2207; (*d*) S. Manzini, A. Poater, D. J. Nelson, L. Cavallo, A. M. Z. Slawin and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2014, **53**, 8995–8999.

26 Reactions involving **37** (X = Cl) with a stoichiometric amount of catalyst **6** were also attempted, however this resulted in a complex mixture.

27 The decomposition pathways involving Ru-methylidene intermediates are documented in the literature. See (*a*) S. H. Hong, A. G. Wenzel, T. T. Salguero, M. W. Day and R. H. Grubbs, *J. Am. Chem. Soc.*, 2007, **129**, 7961–7968; (*b*) M. Ulman and R. H. Grubbs, *J. Org. Chem.*, 1999, **64**, 7202–7207; (*c*) M. S. Sanford, J. A. Love and R. H. Grubbs, *J. Am. Chem. Soc.*, 2001, **123**, 6543–6554; (*d*) K. A. Burdett, L. D. Harris, P. Margl, B. R. Maughon, T. Mokhtar-Zadeh, P. C. Saucier and E. P. Wasserman, *Organometallics*, 2004, **23**, 2027–2047; (*e*) Z. Lysenko, B. R. Maughon, T. Mokhtar-

Zadeh and M. L. Tulchinsky, *J. Organomet. Chem.*, 2006, **691**, 5197–5203; (*f*) S. Monfette, M. Eyholzer, D. M. Roberge and D. E. Fogg, *Chem. – Eur. J.*, 2010, **16**, 11720–11725; (*g*) J. A. Lummiss, N. J. Beach, J. C. Smith and D. E. Fogg, *Catal. Sci. Technol.*, 2012, **2**, 1630–1632.

28 S. Gerritz, S. Shi and S. Zhu, Aminoacetamide Acyl Guanidines as beta-Secretase Inhibitors, *United States Patent US* 2006/0287287, 2006.

29 L. Hintermann, *Beilstein J. Org. Chem.*, 2007, **3**, 22.

30 G. A. Grasa, M. S. Viciu, J. Huang and S. P. Nolan, *J. Org. Chem.*, 2001, **66**, 7729–7737.