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Divergent Approach to a Family of Tyrosine-derived Ru-Alkylidene Olefin Metathesis Catalysts

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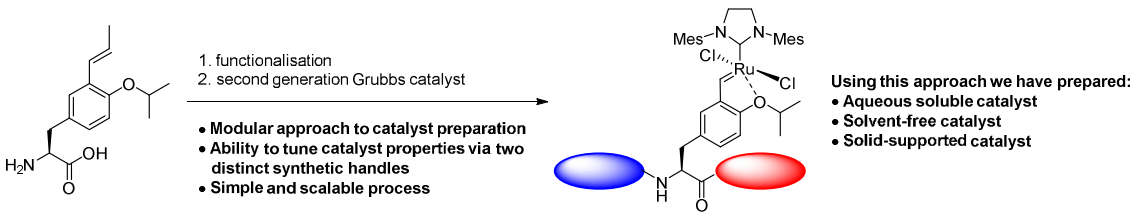


Abstract

A simple and generic approach to access a new family of Ru-alkylidene olefin metathesis catalysts with specialised properties is reported. This strategy utilises a late stage, utilitarian Hoveyda-type ligand derived from tyrosine, which can be accessed *via* a multi-gram scale synthesis. Further functionalisation allows catalyst properties to be tuned, giving access to modified second generation Hoveyda-Grubbs type catalysts. This divergent synthetic approach can be used to access solid-supported catalysts and catalysts that function under solvent-free and aqueous conditions.

Introduction

Olefin metathesis has provided a powerful tool for the formation of C-C bonds.[1] The exceptional functional group tolerance, selectivity and stability of well defined commercially available Ru-alkylidene catalysts such as **1** and **2** (Figure 1) have

allowed application of this reaction to a broad range of substrates.[2] Notable recent developments in this field include *Z*-selectivity,[3] efficient ethenolysis,[4] alternative metal centers[5] and alternative operating solvents.[6] The latter case is of significant importance for developing more environmentally benign olefin metathesis processes.[7] Furthermore, modification of parent architectures has enabled efficient olefin metathesis reactions under aqueous[8] and solvent-free conditions,[9] as well as recoverable or recyclable catalyst systems.[10] To-date, synthetic strategies used to access modified Ru-based catalysts have adopted a target-orientated approach, focusing on incorporating one specific catalyst property (for example water solubility or solid-supported) rather than a generic or divergent approach to access a tuneable catalyst family.

As part of our studies on improving olefin metathesis technology,[11] we envisaged that a rationally designed ligand precursor would allow a divergent and highly tuneable approach to catalyst preparation. We designed Hoveyda-type ligand precursor **3** (Figure 1) to examine this approach. Notably, **3** can be prepared from readily available L-tyrosine and possesses chemically distinguishable amine and carboxylic acid groups for further manipulation. In this paper, we disclose the generality of this strategy through the preparation of three Ru-alkylidene based catalysts **4**-**6**. Specifically, functionalising the amine and carboxylic acid groups with hydrophilic PEG groups should provide a water soluble Ru-complex **4** suitable for olefin metathesis in aqueous media. Conversely, addition of hydrophobic alkane groups onto the amino acid handles should provide a highly organic soluble catalyst **5** suitable for solvent-free conditions. Finally, incorporation of **3** into a solid support *via* solid phase

peptide synthesis (SPPS) should provide access to a potentially recyclable pre-catalyst system **6**.

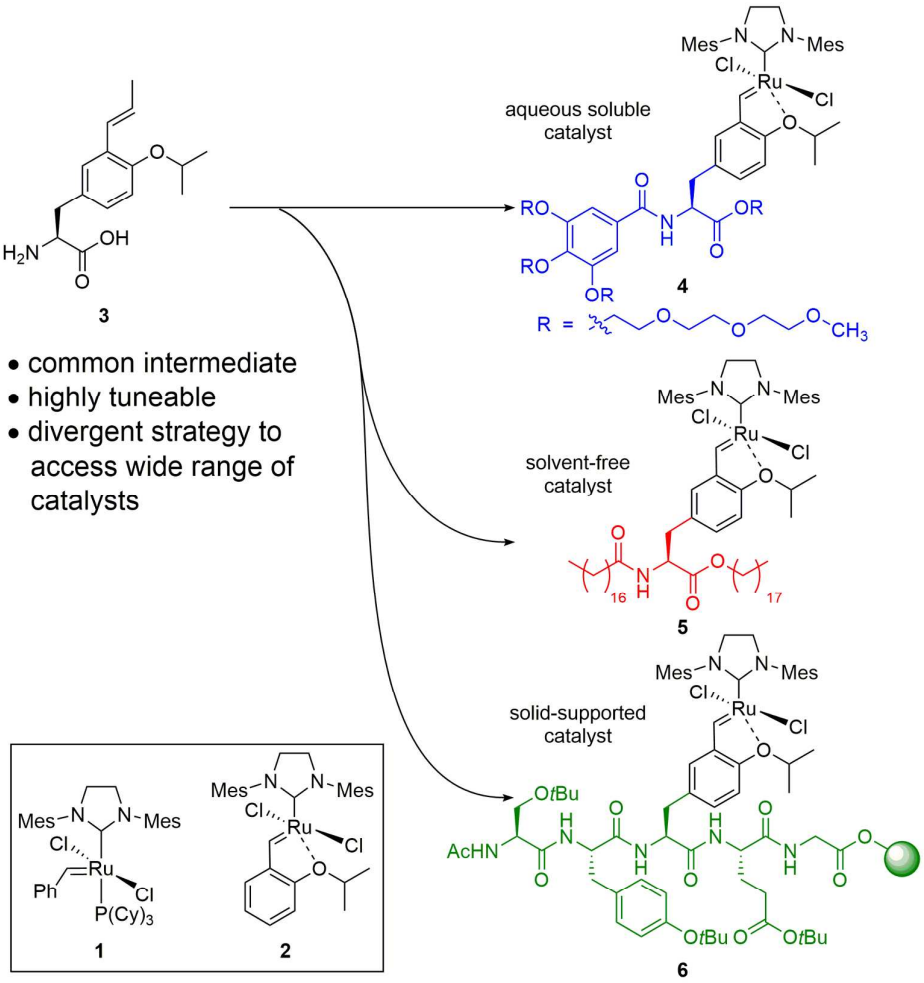
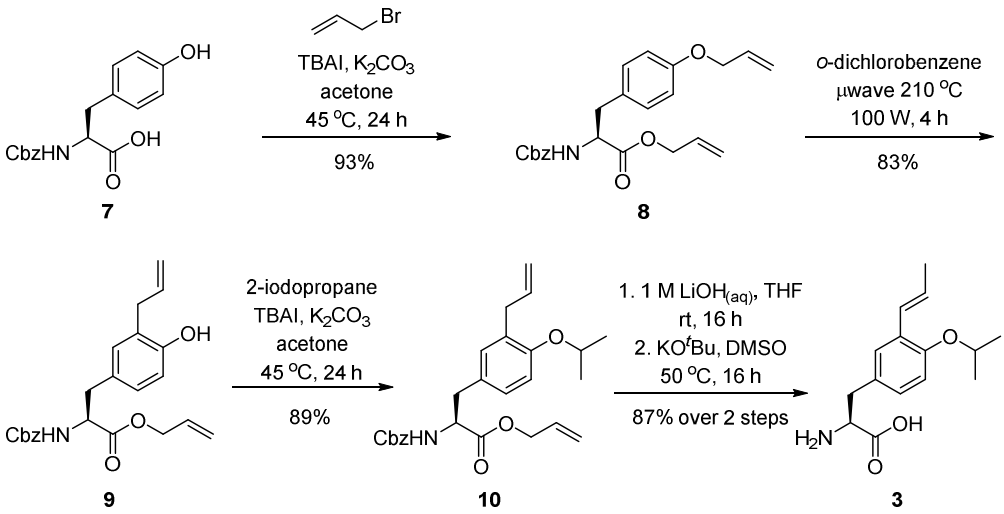


Figure 1 Divergent strategy for synthesis of catalysts **4**, **5** and **6**

Results and Discussion

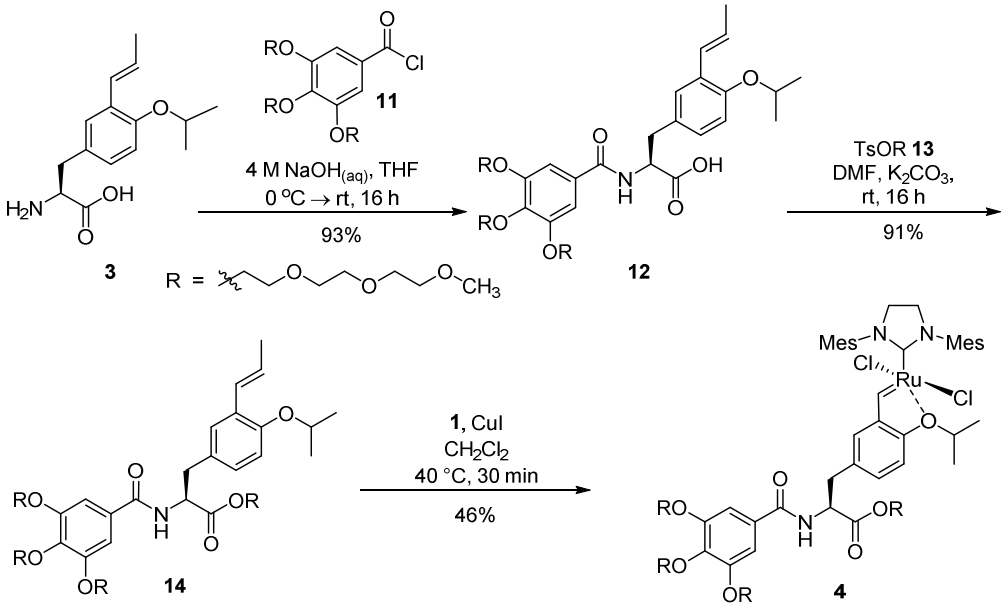
Herein we demonstrate a highly tuneable synthetic strategy to access a range of Ru-based olefin metathesis catalysts through the use of **3** as a common ligand precursor. Studies commenced with the preparation of the parent ligand **3** from commercially available L-tyrosine derivative **7** (Scheme 1). Allylation of **7** with allyl bromide afforded the di-allyl analogue **8**. Thermally induced Claisen rearrangement gave the *ortho*-substituted phenol **9**.[12] Alkylation of **9** with 2-iodopropane delivered the desired

ether **10**. Finally, ester hydrolysis followed by isomerisation/deprotection using KO^{t}Bu provided the *iso*-propoxystyrene ligand **3**, which could be easily accessed on multi-gram scale.



Scheme 1 Preparation of parent ligand precursor **3**.

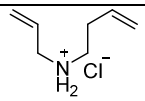
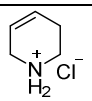
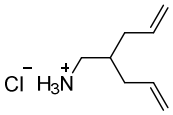
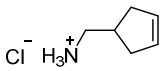
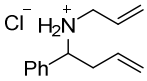
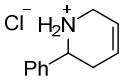
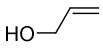
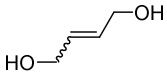
With the key ligand precursor **3** in hand, we sought to utilise the amine and carboxylic acid groups as synthetic handles to tune catalyst properties *via* incorporation of useful functionalities. We first studied tethering hydrophilic functionalities to ligand precursor **3** to access a water soluble Ru-alkylidene catalyst (Scheme 2). Towards this end, **3** was reacted with the acyl chloride **11** to afford the amide **12**. Esterification using the tosylate **13** under basic conditions gave the required ester **14**. Subsequent co-ordination of **14** to catalyst **1** provided the target Ru-alkylidene complex **4**. Purification of **4** was achieved in a straightforward manner *via* alumina column chromatography.



Scheme 2 Preparation of water soluble complex **4**

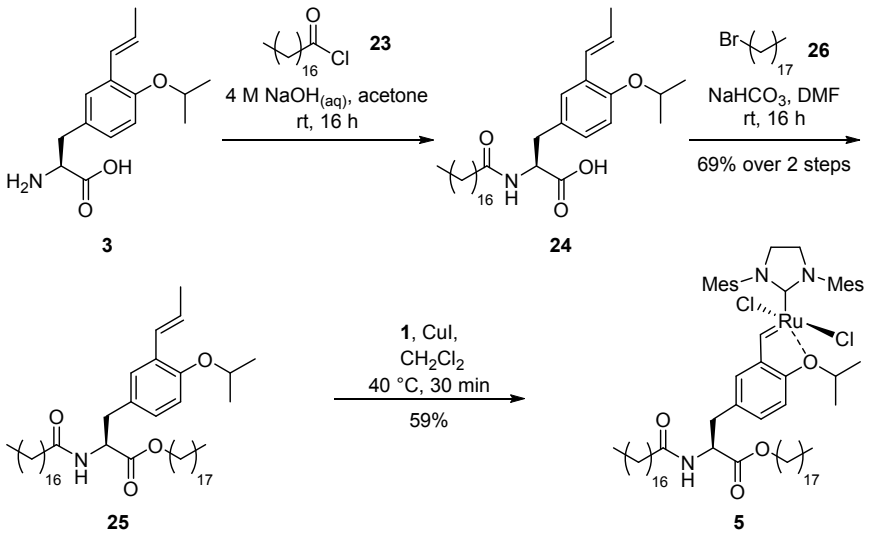
The activity of PEG catalyst **4** was assessed using substrates **15-18** (Table 1). Unfortunately, catalyst **4** showed limited solubility in pure water.[12] Attempted ring-closing metathesis (RCM) of **15** with catalyst **4** in pure water at 40 °C under ultrasonication, gave poor conversion to product **19** (Table 1, Entry 2). However, using a water/methanol mixture (1:1) provided a suitable medium for aqueous metathesis. Using a loading of 2.5 mol% of **4**, the RCM of dienes **15**, **16** and **17** gave complete conversion to cyclised products **19**, **20** and **21** respectively. The cross-metathesis (CM) of allyl alcohol (**18**) also proceeded quantitatively to give the diol **22**.

Table 1 Selected scope for catalyst **4**

Entry	Substrate	Product	Conv. (%)[a]
1	 **15**	 **19**	25[b] >95[c]
2	 **16**	 **20**	>95[c]
3	 **17**	 **21**	>95[c]
4	 **18**	 **22**	>95[c]

[a] Conversions were determined by ^{1}H-NMR spectroscopy. [b] Metathesis reactions were performed using 2.5 mol% **4** under ultrasonication for 2 h then at 40 °C for 16 h. Conversions were determined by ^{1}H-NMR spectroscopy. [c] Metathesis reactions were performed using 2.5 mol% **4** in 1:1 H_2O:MeOH at 40 °C for 16 h.

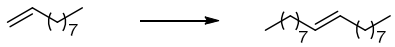
Next, we were interested in transforming styrene **3** into a catalyst suitable for metathesis under solvent-free conditions with highly non-polar substrates. Hence, lipophilic groups were attached to the amine and carboxylic acid termini. Acylation of **3** with stearoyl chloride (**23**) gave amide **24** (Scheme 3). The carboxylic acid was next converted to the ester **25** derivative by treatment with 1-bromooctadecane (**26**) under basic conditions. Finally, co-ordination of **25** to catalyst **1** gave the target lipophilic Ru-alkylidene complex **5**. Notably, complex **5** was prepared from the key precursor **3** in three facile steps.



Scheme 3 Preparation of lipophilic Ru-alkylidene complex **5**

The CM activity of **5** was investigated using solvent-free conditions by studying the dimerisation of 1-decene (**27**). The optimal catalyst loading was studied and compared with the commercially available catalyst **2** (Table 2). Initially, optimisation studies were completed at room temperature (Table 2, entries 1-3). Catalyst **5** showed significantly higher reactivity than catalyst **2** under solvent-free conditions. This can be attributed to the differences in solubility of **5** compared with catalyst **2**. Addition of **5** to 1-decene (**27**) instantly resulted in a homogenous reaction mixture. In contrast, catalyst **2** was largely insoluble in the neat substrate. By elevating the temperature to 40 °C, catalyst loading could be further reduced (Table 2, entries 4-6). Optimal conditions were observed at 0.5 mol% of **5** at 40 °C, providing 91% conversion to the dimerised product **28**.

Table 2 Optimisation of CM conditions using **5**[a]



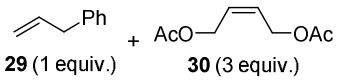
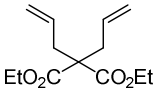
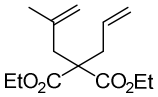
27 **28**

Entry	Loading (mol%)	Temp (°C)	Catalyst **5**[a]	Catalyst **2**[a]
1	1.0	20 (r.t)	83%	11%
2	0.5	20 (r.t)	54%	10%
3	0.1	20 (r.t)	7%	3%
4	0.5	40	91%	-
5	0.25	40	16%	-
6	0.1	40	5%	-

[a] Metathesis reactions were performed using **5** or **2** in neat **27**. Conversions were determined by ^{1}H-NMR spectroscopy.

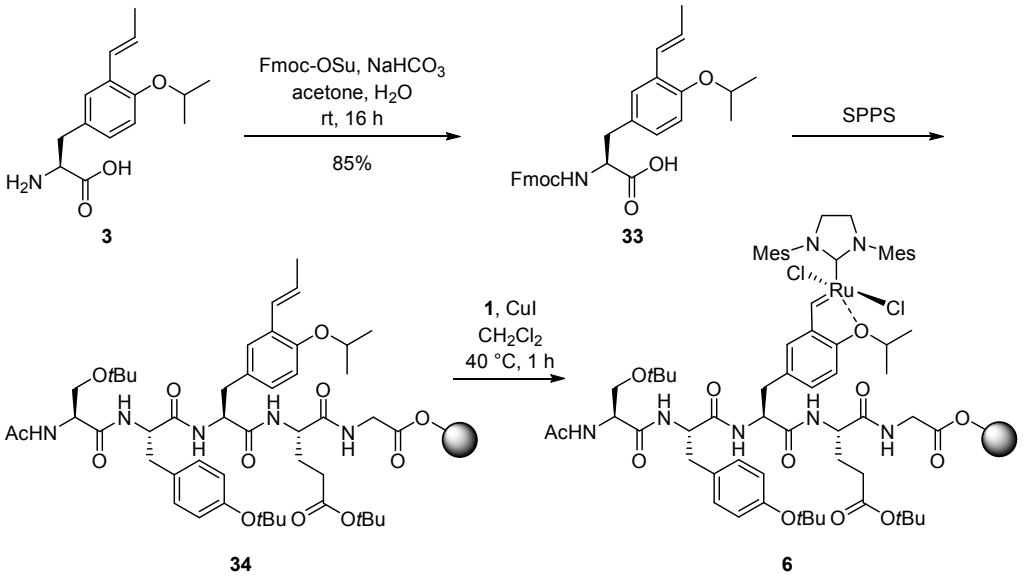
With optimised conditions in hand, we studied the dimerisation of other alkene substrates with catalyst **5** (Table 3). Self-metathesis of homologous terminal alkenes, 1-octene and 1-hexene, provided excellent conversions to their respective cross-products (entries 1-2). High conversions were also observed for the CM of non-polar alcohol ω-undecylenyl alcohol (entry 3) and 1-vinyl cyclohexanol (entry 4). Cross-metathesis between allylbenzene (**29**) and *cis*-1,4-diacetoxy-2-butene (**30**) under solvent-free conditions gave the corresponding cross-product in modest isolated yield (entry 5). Catalyst **5** also mediated good conversion of 1,5-cyclooctadiene in a ring-opening metathesis polymerisation (ROMP) reaction (entry 6). Finally, solvent-free RCM of dienes **31** and **32** both proceeded with excellent conversion without formation of polymeric by-products (entries 7 and 8).

Table 3 Selected scope for catalyst **5**

Entry	Substrate	Conv. (%)[a]
1	1-octene	95
2	1-hexene	>95
3	ω-undecylenyl alcohol	>95
4	1-vinyl cyclohexanol	90
5	 **29** (1 equiv.) + **30** (3 equiv.)	57[b]
6	1,5-cyclooctadiene	83
7	 **31**	>95
8	 **32**	88

[a] Metathesis reactions were performed using 0.5 mol% **5** in neat substrate at 40 °C. Conversions were determined by ^{1}H-NMR spectroscopy. [b] Isolated yield

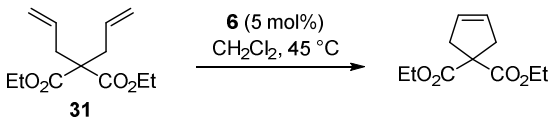
Lastly, we explored the development of a solid-supported recyclable catalyst *via* the incorporation of ligand precursor **3** into a peptide sequence using established SPPS technology. Reaction of **3** with Fmoc-OSu provided the required *N*-Fmoc analogue **33** (Scheme 4). SPPS began with Fmoc-Gly-Wang resin and sequential coupling of Fmoc-Glu, *N*-Fmoc-protected analogue **33**, Fmoc-Tyr, and Fmoc-Ser delivered the solid-supported penta-peptide **34**. Subsequent co-ordination of **34** to catalyst **1** afforded the solid-supported Ru-alkylidene complex **6** as green resin beads.[13]



Scheme 4 Preparation of solid-supported olefin Ru-alkylidene complex **6**

The catalytic activity of **6** was assessed with the RCM reaction of diethyl diallylmalonate **31** (Table 4, entry 1). At 5 mol% loading of **6** the reaction proceeded to 95% after 0.5 h at 45 ^{o}C. Significantly, removal of the solid-supported catalyst from the reaction mixture was achieved *via* a simple filtration of the resin beads; the resulting filtrate was only faintly coloured (Figure 2). In contrast, after an analogous reaction performed using 5 mol% **2**, the resultant reaction mixture was visibly darker due to higher Ru-contamination (Figure 2). The filtered and washed resin-bound catalyst was reused in five subsequent RCM reactions with no loss of activity (Table 4, entries 1-6). Additionally, three more catalyst cycles were performed with extended reaction times to provide excellent ring-closure of diethyl diallylmalonate (**31**) (entries 7-9).[14]

Table 4 RCM of **31** catalysed by a single batch of resin-bound catalyst **6**



31

Runs	Time (h)	Conv. (%)[a]	Ru (ppm)[b]
1	0.5	95	45
2	0.5	95	45
3	0.5	95	33
4	1	95	36
5	1	95	24
6	1	95	12
7	1.5	92	19
8	1.5	90	20
9	2	90	16

[a] Metathesis reactions were performed using 5 mol% **6** in CH_2Cl_2 at 45 °C. Conversions were determined by ^{1}H-NMR spectroscopy. A single batch of catalyst **6** was used across runs 1-9. [b] Ru analysis performed using ICP-MS.

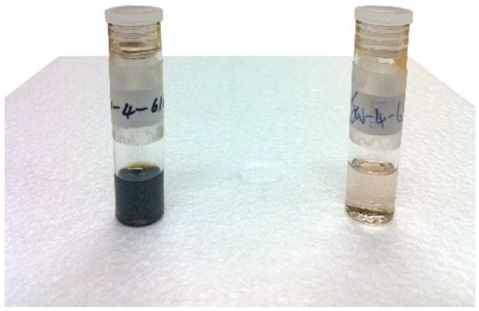


Figure 2 left) RCM reaction of **31** using 5 mol% **2** and right) RCM reaction of **31** using 5 mol% **6** (after filtration)

The attachment of the Ru-complex to the solid support *via* the labile Hoveyda ligand relies on a catch-release or 'boomerang' mechanism, which is still widely disputed.[15] If this mechanism is highly operational yet inefficient, such catalysts can potentially suffer from significant leaching of the active Ru species into the reaction medium. Consequently, we were also interested in determining the amount of Ru contaminant present in the product. Ru analysis of the filtrate from each reaction (entries 1-9) was performed using ICP-MS (Table 4). Our results show a sustained leaching of Ru into the reaction medium, losing a total of 20% of the initial Ru content over the nine reaction cycles. This amount of leaching is comparable with supported Ru-alkylidene catalysts previously reported by Lee and coworkers[10d] and Bannwarth and coworkers.[10j]

Conclusions

In summary, a generic and simple approach has been developed to prepare a family of specialist Ru-alkylidene catalysts for olefin metathesis. Preparation of the key ligand precursor **3** was achieved *via* five facile and high yielding steps from commercially available L-tyrosine **7**. Further functionalization of **3** provides access to modified second generation Hoveyda-Grubbs type catalysts. Through this single synthetic approach, ruthenium alkylidene catalysts for use in solvent-free reactions, aqueous media and recycling have been prepared. We envisage that this general strategy could be adopted by other organic synthesis research groups in need of bespoke olefin metathesis catalysts. Current work is underway to utilise this generic approach to

access other tailored catalyst systems which may address current synthetic challenges of olefin metathesis.

Experimental Section

Dichloromethane (CH_2Cl_2) was distilled over CaH_2 prior to use. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled over potassium prior to use. Acetic acid (AcOH), acetone, dimethylformamide (DMF) ethyl acetate (EtOAc), hexane and methanol (CH_3OH), copper(I) chloride (CuCl), Cbz-L-tyrosine, *o*-dichlorobenzene, dimethyl sulfoxide (DMSO), 2-iodopropane, potassium *tert*-butoxide (KO^tBu), stearic acid were used as supplied. Benzylidene [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium was used as supplied by Sigma-Aldrich.

Allyl (*S*)-3-(4-(allyloxy)phenyl)-2-(((benzyloxy)carbonyl)amino)propanoate 8

Potassium carbonate (17.5 g, 127 mmol) and allyl bromide (11.0 mL, 15.4 g, 127 mmol) were added to a solution of Cbz-L-tyrosine **7** (10.0 g, 31.7 mmol) in acetone (150 mL). The reaction mixture was vigorously stirred for 5 min before TBAI (11.7 g, 31.7 mmol) was added in portions over 20 min. The resulting suspension was then sealed and heated at 45 °C for 48 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The colourless residue was resuspended in EtOAc (200 mL), filtered and the filtrate concentrated under reduced pressure. The residue was then purified by silica chromatography (8:1, hexane:EtOAc) to give titled compound **8** as a colourless solid (11.7 g, 93%), m.p. 36.9-38.6 °C. IR ν_{max} 3345m, 3067m, 3033m, 2937m, 1718s, 1611m, 1509s, 1455m,

1239s, 1219s, 1177s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H), 7.03-7.00 (m, 2H), 6.84-6.80 (m, 2H), 6.05 (ddt, *J* = 17.2, 10.4, 5.4 Hz, 1H), 5.92-5.82 (m, 1H), 5.44-5.24 (m, 5H), 5.14-5.07 (m, 2H), 4.68-4.61 (m, 3H), 4.51 (dt, *J* = 5.4, 1.2 Hz, 2H), 3.12-3.02 (m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 171.4, 157.8. 155.7, 136.3, 133.3, 131.5, 130.4, 128.6, 128.2, 128.1, 127.8, 119.1, 117.7, 114.9, 68.8, 67.0, 66.0, 55.0, 37.4. HRMS (ESI^+, MeOH): *m/z* 396.1801 $[M + H]^+$, $C_{23}H_{26}NO_5^+$ requires 396.1805.

Allyl (*S*)-3-(3-allyl-4-hydroxyphenyl)-2-(((benzyloxy)carbonyl)amino)propanoate 9

Compound **9** was prepared according to a modified procedure by Grela and coworkers.[14] A solution of ether **8** (9.34 g, 23.6 mmol) in *o*-dichlorobenzene (20 mL) was added to a microwave vessel. The vessel was thoroughly flushed with nitrogen, sealed and irradiated (100 W, 210 °C) for 4 h. The resultant reaction mixture was concentrated under reduced pressure and the residue was then purified by silica column chromatography (3:1, hexane:EtOAc) to give titled compound **9** as a colourless oil (7.78 g, 83%). IR ν_{max} 3356brs, 3070m, 3032m, 2945m, 1696s, 1508s, 1438m, 1340m, 1260s, 1189s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H), 6.85-6.82 (m, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.02-5.85 (m, 2H), 5.37-5.25 (m, 3H), 5.15-5.06 (m, 4H), 4.68-4.61 (m, 3H), 3.39-3.30 (m, 2H), 3.09-2.99 (m, 2H) (OH not observed due to exchange). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 171.6, 155.9, 153.4, 136.5, 136.2, 131.5, 131.2, 128.6, 128.4, 128.3, 128.1, 127.4, 126.0, 119.1, 116.2, 115.8, 67.2, 66.2, 55.1, 37.5, 34.6. HRMS (ESI^+, MeOH): *m/z* 396.1801 $[M + H]^+$, $C_{23}H_{26}NO_5^+$ requires 396.1805.

Allyl (*S*)-3-(3-allyl-4-isopropoxyphenyl)-2-(((benzyloxy)carbonyl) amino)propanoate 10

Compound **10** was prepared according to a modified procedure by Grela and coworkers.[14] Potassium carbonate (10.6 g, 76.9 mmol) and 2-iodopropane (4.80 mL, 8.17 g, 48.1 mmol) were added to a stirred solution of the phenol **9** (7.58 g, 19.2 mmol) in acetone (100 mL). The reaction mixture was vigorously stirred for 5 min before TBAI (7.10 g, 19.2 mmol) was added in portions over 10 min. The resultant suspension was sealed and heated to 45 °C for 24 h. The reaction mixture was concentrated under reduced pressure. The residue was resuspended in EtOAc (100 mL), filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica column chromatography (9:1, hexane:EtOAc) to give titled compound **10** as a colourless oil (6.75 g, 80%). IR ν_{max} 3338brs, 3067m, 2976m, 2936m, 1719s, 1496s, 1454m, 1382m, 1339m, 1246s, 1189m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H), 6.90-6.86 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.98-5.82 (m, 2H), 5.33-4.99 (m, 7H), 4.66-4.60 (m, 3H), 4.51 (sept, *J* = 6.0 Hz, 1H), 3.36-3.26 (m, 2H), 3.04 (d, *J* = 5.6 Hz, 2H), 1.32 (d, *J* = 6.0 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.5, 155.8, 154.9, 137.1, 136.5, 131.7, 131.0, 130.0, 128.6, 128.3, 128.2, 128.0, 127.2, 119.0, 115.5, 113.1, 70.2, 67.0, 66.1, 55.1, 37.5, 34.5, 22.3. HRMS (ESI^+, MeOH): *m/z* 438.2288 $[M + H]^+$, $C_{26}H_{32}NO_5^+$ requires 438.2275.

(*S*,*E*)-2-Amino-3-(4-isopropoxy-3-(prop-1-en-1-yl)phenyl)propanoic acid 3

An aqueous solution of 1 M LiOH (15 mL) was added to **10** (0.50 g, 1.1 mmol) in THF (15 mL) and the mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated to half volume under reduced pressure, acidified to pH 2 with aqueous 1 M HCl and extracted with EtOAc (3 x 50 mL). The combined organic

layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was then redissolved in DMSO (26 mL). KO^{t}Bu (0.58 g, 5.2 mmol) was added and the resultant mixture was stirred at 50 ^oC for 16 h. The mixture was concentrated under reduced pressure. The residue was dissolved in H_2O (5 mL) and 1 M HCl was added to reach pH 6. The precipitate was collected by filtration and washed with H_2O (10 mL) and Et_2O (10 mL) to provide titled compound **3** as a yellow solid (0.26 g, 87%), m.p. 187.4-189.1°C. IR ν_{max} 3448brs, 3200brs, 3038s, 2975s, 2933m, 2913m, 1605s, 1586s, 1489s, 1437m, 1397s, 1332s, 1242s, 1110s, 954s cm^{-1}. ^1H NMR (400 MHz, MeOD): δ 7.36 (d, *J* = 2.2 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.67 (dq, *J* = 15.8, 1.6 Hz, 1H), 6.28 (dq, *J* = 15.8, 6.8 Hz, 1H), 4.55 (sept, *J* = 6.0 Hz, 1H), 3.73 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.23 (dd, *J* = 14.6, 4.0 Hz, 1H), 2.93 (dd, *J* = 14.6, 8.8 Hz, 1H), 1.87 (dd, *J* = 6.8 Hz, 1.6 Hz, 3H), 1.31 (d, *J* = 6.0 Hz, 6H) (COOH and NH_2 not observed due to exchange). $^{13}C\{^1H\}$ NMR (100 MHz, MeOD): δ 173.9, 155.3, 129.9, 129.6, 129.1, 128.5, 127.1, 127.0, 116.0, 72.0, 57.7, 37.6, 22.5, 19.0. HRMS (ESI^-, MeOH): *m/z* 262.1445 $[M - H]^-$, $C_{15}H_{20}NO_3^-$ requires 262.1448.

(*S*,*E*)-3-(4-Isopropoxy-3-(prop-1-en-1-yl)phenyl)-2-(3,4,5-tris(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzamido)propanoic acid 12

Thionyl chloride (1.00 mL, 13.8 mmol) was added to 3,4,5-tris(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzoic acid (1.14 g, 1.87 mmol) and the mixture was sonicated for 1.5 h. Excess $SOCl_2$ was removed under reduced pressure to provide acid chloride **11**. In a separate round bottom flask, an aqueous solution of 2 M NaOH (7 mL) was added to amino acid **3** (0.70 g, 2.6 mmol) in THF (7 mL) at 0 °C. Acid chloride **11** in THF (5 mL) was added dropwise to the amino acid **3** solution. The

reaction mixture was allowed to warm to room temperature and stirred for 16 h. The solution was acidified to pH 1 with aqueous 1 M HCl and THF was removed under reduced pressure. The aqueous solution was extracted with EtOAc (3 x 100 mL), and the combined organic extract was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (100:5:1, CH_2Cl_2:MeOH:AcOH) to give titled compound **12** (1.49 g, 93%) as a yellow oil. IR ν_{max} 2912s, 2874s, 1735m, 1638w, 1580m, 1491m, 1347m, 1243m, 1201m, 1094s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 1.6 Hz, 1H), 6.95-6.94 (m, 4H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.60 (dq, *J* = 16.0. 1.6 Hz, 1H), 6.08 (dq, *J* = 16.0, 6.8 Hz, 1H), 4.87 (q, *J* = 6.4 Hz, 1H), 4.42 (sept, *J* = 6.2 Hz, 1H), 4.17-4.07 (m, 6H), 3.79 (t, *J* = 4.8 Hz, 4H), 3.75 (t, *J* = 5.2 Hz, 2H), 3.70-3.66 (m, 6H), 3.63-3.59 (m, 12H), 3.53-3.50 (m, 6H), 3.34 (s, 3H), 3.33 (s, 6H), 3.23-3.07 (m, 2H), 1.79 (dd, *J* = 6.8, 1.6 Hz, 3H), 1.28 (d, *J* = 6.2 Hz, 6H) (COOH not observed due to exchange). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.7, 167.1, 153.7, 152.5, 141.6, 129.0, 128.5, 128.2, 128.1, 127.6, 126.1, 125.8, 114.4, 107.1, 72.4, 72.0, 70.8, 70.73, 70.68, 70.64, 70.57, 70.54, 70.52, 70.4, 69.8, 69.0, 59.0, 54.3, 36.5, 22.30, 22.28, 19.0 (1 carbon environments overlapping). HRMS (ESI^+, MeOH): *m/z* 876.4349 $[M + Na]^+$, $C_{43}H_{67}NO_{16}Na^+$ requires 876.4358.

2-(2-(2-Methoxyethoxy)ethoxy)ethyl (*S*,*E*)-3-(4-isopropoxy-3-(prop-1-en-1-yl)phenyl)-2-(3,4,5-tris(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzamido)propanoate 14

K_2CO_3 (71.0 mg, 520 μmol) was added to a solution of **12** (120 mg, 141 μmol) and tosylate **13** (49.0 mg, 150 μmol) in DMF (3 mL). The reaction was stirred at room temperature for 16 h. The mixture was diluted with H_2O (50 mL) and extracted with

EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% (w/v) aqueous $CuSO_4$ (2 x 50 mL), H_2O (1 x 50 mL) and brine (1 x 50 mL), then dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (20:1, CH_2Cl_2:MeOH) to give titled compound **14** (128 mg, 91%) as a colourless oil. IR ν_{max} 2873brs, 1741m, 1662m, 1582m, 1490m, 1450w, 1490m, 1350m, 1243m, 1095s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 2.2 Hz, 1H), 6.92 (s, 2H), 6.89 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.59 (dq, *J* = 16.0, 1.6 Hz, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 6.06 (dq, *J* = 16.0, 6.4 Hz, 1H), 4.97-4.92 (m, 1H), 4.43 (sept, *J* = 6.4 Hz, 1H), 4.28-4.25 (m, 2H), 4.15-4.09 (m, 6H), 3.81-3.73 (m, 6H), 3.68-3.65 (m, 8H), 3.61-3.57 (m, 18H), 3.50-3.47 (m, 8H), 3.32 (s, 3H), 3.31 (s, 6H), 3.30 (s, 3H), 3.16 (A of ABX, *J* = 13.8, 5.6 Hz, 1H), 3.10 (B of ABX, *J* = 13.8, 5.6 Hz, 1H), 1.79 (dd, *J* = 6.6, 1.6 Hz, 3H), 1.28 (dd, *J* = 6.2 Hz, 1.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.7, 166.4, 153.7, 152.5, 152.3, 141.6, 129.2, 128.4, 128.1, 128.0, 127.7, 127.5, 126.0, 125.8, 114.3, 106.8, 101.7, 72.4, 71.9, 70.8, 70.7, 70.61, 70.55, 70.5, 69.7, 69.0, 68.8, 64.5, 59.0, 53.7, 36.9, 22.22, 22.20, 18.9 (6 carbon environments overlapping). HRMS (ESI^+, MeOH): *m/z* 1022.5286 $[M + Na]^+$, $C_{50}H_{81}NO_{19}Na^+$ requires 1022.5300.

Aqueous Catalyst 4

Complex **1** (143 mg, 168 μmol), CuCl (17.0 mg, 171 μmol) and **14** (171 mg, 171 μmol) in CH_2Cl_2 (2 mL) were added to a flame-dried Schlenk vessel under N_2 atmosphere. The reaction was stirred at 45 °C for 0.5 h. The dark green mixture was concentrated under reduced pressure and the residue was purified by neutral alumina column chromatography using a N_2 flow (16:4:1 Et_2O:hexane:MeOH) to yield complex **4** (115 mg, 46%) as a green oil. IR ν_{max} 3339w, 2872s, 1739m, 1655m,

1581m, 1485s, 1449m, 1421m, 1256m, 1095s, 1029s cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 16.48 (s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.14 (s, 2H), 7.00-6.92 (m, 5H), 6.71 (d, *J* = 2.0 Hz, 1H), 4.93-4.93 (m, 1H), 4.73-4.68 (m, 1H), 4.29-4.27 (m, 4H), 4.18-4.16 (m, 8H), 3.89-3.84 (m, 6H), 3.76-3.72 (m, 6H), 3.71-3.62 (m, 16H), 3.60-3.48 (m, 12H), 3.37 (s, 3H), 3.36 (s, 6H), 3.35-3.34 (m, 2H), 3.33 (s, 3H), 2.54-2.35 (m, 18H), 1.23 (dd, *J* = 6.0, 1.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, CD_3OD): δ 298.1, 211.2, 172.7, 168.8, 153.9, 153.7, 152.6, 146.7, 142.5, 140.1, 132.5, 131.6, 131.0, 130.3, 130.0, 123.8, 114.4, 107.8, 76.4, 73.7, 73.6, 73.0, 72.9, 71.7, 71.64, 71.56, 71.5, 71.4, 70.8, 70.0, 69.9, 65.7, 59.1, 56.3, 36.2, 22.5, 21.7, 21.3 (8 carbon environments overlapping). HRMS (ESI^+, MeOH): *m/z* 1472.5513 $[M + Na]^+$, $C_{69}H_{103}Cl_2N_3NaO_{19}Ru^{102+}$ requires 1472.5504.

General Procedure for Olefin Metathesis in water/MeOH mixture using Catalyst 4

The complex **4** (7.5 mg, 0.052 mmol, 0.25 mol%) was dissolved in degassed MeOH (1 mL) and added to a solution of substrate (0.21 mmol) in degassed H_2O (1 mL). The homogenous mixture was stirred at 40 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in D_2O and analysed by ^1H NMR spectroscopy.

Octadecyl (*S*,*E*)-3-(4-isopropoxy-3-(prop-1-en-1-yl)phenyl)-2-*N*-(oxooctadecyl)aminopropanoate 25

Thionyl chloride (361 μL, 592 mg, 4.98 mmol) was added to stearic acid (118 mg, 0.42 mmol) and the mixture was sonicated for 1.5 h. Excess $SOCl_2$ was removed under reduced pressure to provide acid chloride **23**. In a separate round bottom flask, amino acid **3** (100 mg, 0.38 mmol) and NaOH (61 mg, 1.52 mmol) were dissolved in

a H_2O (5 mL) and acetone (3 mL) mixture. A solution of **23** in acetone (3mL) was added to the reaction mixture at room temperature. The reaction was stirred for 16 h. The mixture was then acidified with aqueous 1 M HCl until pH 2 and extracted with EtOAc (3 x 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure to give amide **24** which was used in the subsequent step without further purification. $NaHCO_3$ (128 mg, 1.52 mmol) and 1-bromooctadecane (253 mg, 0.76 mmol) were added at room temperature to a solution of **24** in DMF (3 mL). The reaction was stirred at room temperature for 16 h. The mixture was diluted with H_2O (50 mL) and was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (2 x 50 mL) and brine (1 x 50 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica column chromatography (11:1, hexane:EtOAc) to afford titled compound **25** as a colourless solid (206 mg, 69%), m.p. 69.2 – 72.5 ^oC. IR ν_{max} 3254w, 2914s, 2849s, 1736m, 1638m, 1542m, 1491m, 1467m, 1372w, 1244s, 1112m, 967m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.66 (dq, *J* = 15.6, 1.6 Hz, 1H), 6.16 (dq, 15.6, 6.6 Hz, 1H), 5.88 (d, *J* = 8.0 Hz, 1H), 4.84 (dt, *J* = 7.7, 5.6 Hz, 1H), 4.47 (sept, *J* = 6.0 Hz, 1H), 4.11-4.06 (m, 2H), 3.04 (d, *J* = 6.0 Hz, 2H), 2.18-2.15 (m, 2H), 1.88 (dd, *J* = 6.6, 1.6 Hz, 3H), 1.60-1.57 (m, 4H), 1.33 (d, *J* = 6.0 Hz, 6H), 1.29-1.22 (m, 58H), 0.89-0.86 (m 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 172.7, 172.1, 153.9, 128.4, 128.3, 127.9, 127.6, 126.1, 126.0, 114.4, 71.0, 65.8, 53.2, 37.5, 36.8, 32.1, 29.85, 29.81, 29.76, 29.7, 29.6, 29.5, 29.44, 29.40, 28.7, 26.0, 25.8, 22.8, 22.4, 19.0, 14.2 (19 overlapping carbon environments). HRMS (ESI^+, MeOH): *m/z* 782.7018 $[M + H]^+$, $C_{51}H_{92}NO_4^+$ requires 782.7026.

Solvent-Free Catalyst 5

Complex **1** (100 mg, 0.116 mmol), CuCl (12.7 mg, 0.128 mmol) and a solution of **25** (100 mg, 0.113 mmol) in CH_2Cl_2 (4 mL) were added to a flame-dried Schlenk vessel under N_2 atmosphere. The reaction was stirred at 45 °C for 0.5 h. The dark green mixture was concentrated under reduced pressure and the residue was purified by silica column chromatography using a N_2 flow (4:1, hexane:Et_2O → 1:4, hexane:Et_2O) to give complex **5** as a green solid (108 mg, 69%), m.p. 120.6 – 127.8 ^oC. IR ν_{max} 3320w, 2920s, 2851s, 1736m, 1672m, 1518m, 1487m, 1420m, 1262s, 1221m, 1198m, 1133m, 1105m cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ 16.70 (s, 1H), 7.16 (m, 4H), 7.10 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.03 (s, 2H), 6.97-6.96 (m, 3H), 6.34 (d, *J* = 8.4 Hz, 1H), 5.57 (d, *J* = 7.6 Hz, 1H), 5.02-4.96 (m, 1H), 4.48 (sept, *J* = 6.4 Hz, 1H), 4.03-4.39 (m, 2H), 3.44 (s, 4H), 3.17-3.08 (m, 2H), 2.59-2.40 (m, 18H), 1.83-1.66 (m, 4H), 1.64-1.58 (m, 2H), 1.36-1.25 (m, 60H), 0.94-0.90 (m, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, C_6D_6): δ 292.0, 212.7, 172.3, 171.9, 151.7, 145.9, 138.9, 130.5, 129.8, 129.3, 128.5, 127.6, 123.5, 113.0, 75.2, 65.5, 54.1, 51.3, 37.4, 36.2, 32.4, 30.27, 30.25, 30.2, 30.1, 30.0, 29.9, 29.7, 29.6, 28.8, 26.2, 25.9, 23.2, 21.4, 21.3, 14.4 (20 overlapping carbon environments). HRMS (ESI^+, MeOH): *m/z* 1254.7068 $[M + Na]^+$, $C_{70}H_{113}Cl_2N_3NaO_4Ru^+$ requires 1254.7044.

General Procedure for Solvent-Free Olefin Metathesis using Catalyst 5

The complex **5** (3.0 mg, 0.002 mmol, 0.5 mol%) was added to the neat substrate (0.49 mmol) under an inert atmosphere and heated at 40 °C for 16 h. The reaction mixture was dissolved in $CDCl_3$ and analysed by ^1H NMR spectroscopy.

(*E*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-isopropoxy-3-(prop-1-en-1-yl)phenyl)propanoic acid 33

Amino acid **3** (200 mg, 759 μmol) and $NaHCO_3$ (255 mg, 3.04 mmol) were dissolved in a mixture of H_2O (7.5 mL) and acetone (3 mL). A solution of Fmoc-OSu (230 mg, 722 μmol) in acetone (4.5 mL) was added at room temperature and the reaction was stirred for 16 h. The mixture was acidified to pH 2 with aqueous 1 M HCl and acetone was removed under reduced pressure. The resulting solution was extracted with EtOAc (40 mL) and organic phase washed with brine (40 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (60:40:1, hexane:EtOAc:AcOH) to give titled compound **33** as a colourless solid (315 mg, 85%). IR ν_{max} 3294m, 3067w, 2984w, 2850w, 1691s, 1543m, 1490m, 1430m, 1297m, 1247s, 735s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.32-7.27 (m, 2H), 7.22 (s, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.66 (dd, *J* = 15.8, 1.6 Hz, 1H), 6.19 (dq, *J* = 15.8, 6.6 Hz, 1H), 5.21 (d, *J* = 8.0 Hz, 1H), 4.70-4.65 (m, 1H), 4.50-4.32 (m, 3H), 4.20 (t, *J* = 7.2 Hz, 1H), 3.16 (A of ABX, *J* = 14.2, 6.4 Hz, 1H), 3.06 (B of ABX, *J* = 14.2, 6.4 Hz, 1H), 1.85 (dd, *J* = 6.6, 1.6 Hz, 3H), 1.33 (d, *J* = 6.0 Hz, 6H) (COOH not observed due to exchange). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.3, 154.1, 143.9, 141.4, 141.3, 128.53, 128.55, 127.9, 127.5, 127.4, 127.2, 126.5, 125.9, 125.2, 120.1, 114.5, 71.0, 67.4, 54.8, 47.3, 37.2, 22.4, 19.1. HRMS (ESI^+, MeOH): *m/z* 508.2092 $[M + Na]^+$, $C_{30}H_{31}NO_5Na^+$ requires 508.2094.

Peptide ligand 34

Manual Fmoc SPPS of **34** (0.05 mmol) was performed in polypropylene Terumo syringes (5 mL) fitted with a porous polyethylene filter. Fmoc-Gly-Wang resin was swollen with CH_2Cl_2/DMF (1:1) prior to synthesis. Sequential deprotection (20%v/v piperadine in DMF), coupling (0.05 mmol amino acid, 0.05 mmol HATU, 0.10 mmol NMM, 3 mL DMF) and final capping (94:5:1, DMF:Ac_2O:NMM) provided the desired solid-supported peptide **34**. LRMS (ESI^+, MeCN:H_2O:HCOOH): *m/z* 742.3 $[M + H]^+$, $C_{36}H_{48}N_5O_{12}^+$ requires 742.3. RP-HPLC (Agilent Vydac C18 analytical column, 15-50% MeCN over 35 min): t_R = 12.7 min.

Solid-supported catalyst 6

Copper (I) chloride (3 mg, 0.030 mmol) and **1** (30 mg, 0.035 mmol) were added to a stirred suspension of **34** (0.030 mmol) in CH_2Cl_2 (2 mL) under an atmosphere of N_2. The flask was heated to 45 °C for 1 h. The suspension was filtered *via* canula and the resin beads washed (3 x 5 mL) with fresh CH_2Cl_2. The resin beads were dried under vacuum to afford **6** as a green solid. LRMS (ESI^+, MeOH): 1193.3 *m/z* $[M + H]^+$, $C_{55}H_{70}N_7O_{12}Ru^{102+}$ requires 1192.3.

General Procedure for Olefin Metathesis using Solid-Supported Recyclable Catalyst 6

A degassed solution of diethyl diallylmalonate **31** (0.12 mL, 0.5 mmol) in CH_2Cl_2 (2 mL) was added to the supported catalyst **6** (0.025 mmol, 5 mol%). The mixture was stirred at 45 °C for 0.5-2 h. Removal of the catalyst **6** from the reaction was achieved *via* canula filtration. The solid-supported catalyst was washed further with CH_2Cl_2 (2 x 5 mL) and dried *in vacuo*. The resultant filtrate was concentrated *in vacuo*,

dissolved in $CDCl_3$ and analysed by ^1H NMR spectroscopy. The filtrate was diluted in MQ H_2O (100 mL) and Ru content analysed by ICP-MS.

Associated Content

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Notes

The authors declare no competing financial interest

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Supporting Information

Copies of ^1H, $^{13}C\{^1H\}$ NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

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12. Grubbs and co-workers[8g] generate water soluble Ru-alkylidene catalyst using longer PEG motifs (Mn ~ 2639). PEG-based catalyst system **4** employs shorter PEG chains. This aids chromatographic purification but may result in lower water solubility.
13. The peptide sequence is of significant importance to the overall activity and recyclability of the resultant catalyst. Incorporation of **3** at the *N*-terminus resulted in a catalyst possessing high activity (e.g. RCM of **31**) but poor recyclability.
14. Catalyst **6** was also prepared using 0.5 equivalents of **1** to ligand **34**. RCM of **31** using 5 mol% of Ru was conducted and showed a decline in catalyst activity and recyclability.
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