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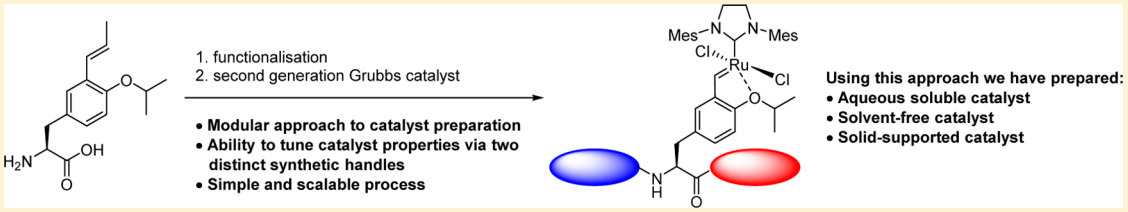
# Divergent Approach to a Family of Tyrosine-Derived Ru−Alkylidene Olefin Metathesis Catalysts

Ellen C. Gleeson, Zhen J. Wang, W. Roy Jackson, and Andrea J. Robinson*

School of Chemistry, Monash University, Clayton, Victoria 3800, Australia

Supporting Information




**ABSTRACT:** A simple and generic approach to access a new family of Ru−alkylidene olefin metathesis catalysts with specialized properties is reported. This strategy utilizes a late stage, utilitarian Hoveyda-type ligand derived from tyrosine, which can be accessed via a multigram-scale synthesis. Further functionalization allows the 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 tunable 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 tunable 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, functionalizing 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 precatalyst system (**6**).

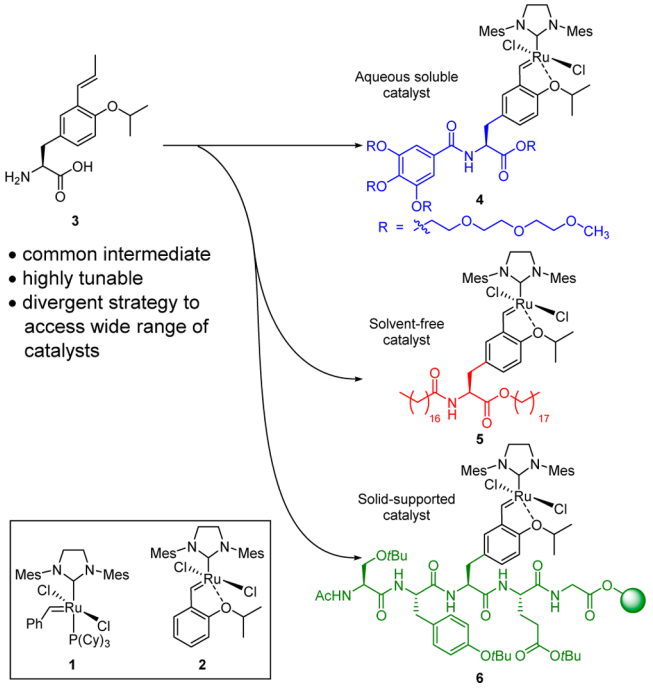



**Figure 1.** Divergent strategy for synthesis of catalysts **4**−**6**.

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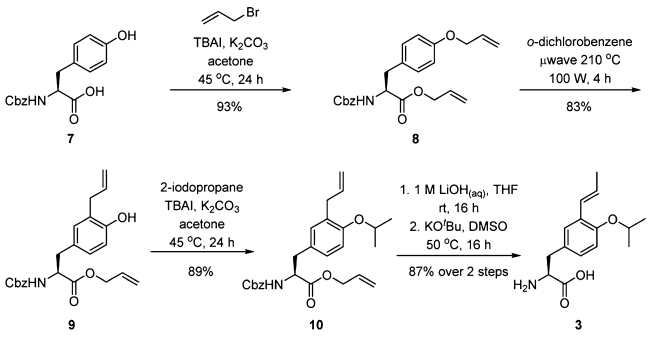
## RESULTS AND DISCUSSION

Herein, we demonstrate a highly tunable 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**

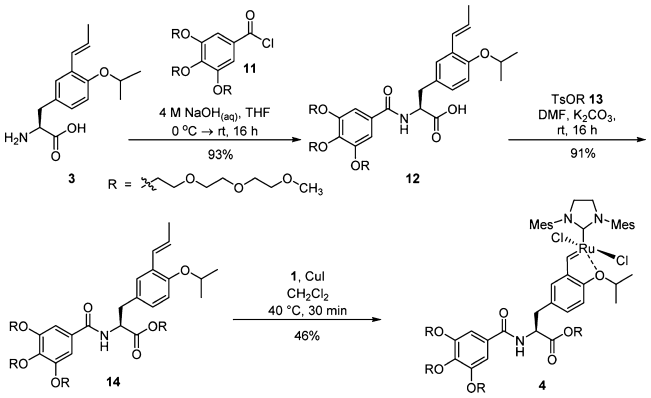
**Scheme 1. Preparation of Parent Ligand Precursor 3**




with allyl bromide afforded the diallyl 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 isomerization/deprotection using KO$^t$Bu provided the *iso*-propoxystyrene ligand **3**, which could be easily accessed on multigram scale.

With the key ligand precursor **3** in hand, we sought to utilize the amine and carboxylic acid groups as synthetic handles to tune the 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). Toward this end, **3** was reacted

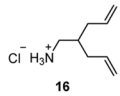
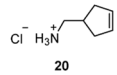
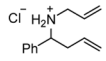
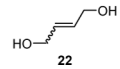
**Scheme 2. Preparation of Water-Soluble Complex 4**




with the acyl chloride **11** to afford the amide **12**. Esterification using the tosylate **13** under basic conditions gave the required ester **14**. Subsequent coordination 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.

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 1). However, using a water/methanol mixture (1:1)

**Table 1. Selected Scope for Catalyst 4**

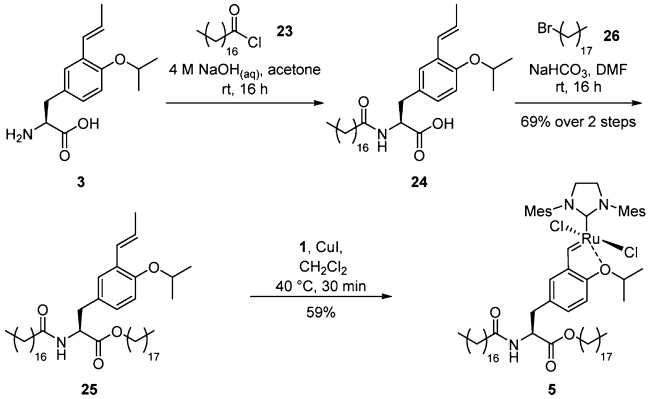
| entry | substrate | product | conv. (%) |
|---|---|---|---|
| 1 |  15 |  19 | 25[b] >95[c] |
| 2 |  16 |  20 | >95[c] |
| 3 |  17 |  21 | >95[c] |
| 4 |  18 |  22 | >95[c] |

[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.

provided a suitable medium for aqueous metathesis. By using a loading of 2.5 mol % **4**, the RCM of dienes **15**–**17** gave complete conversion to cyclized products **19**–**21**, respectively. The cross-metathesis (CM) of allyl alcohol (**18**) also proceeded quantitatively to give the diol **22**.

Next, we were interested in transforming styrene **3** into a catalyst suitable for metathesis under solvent-free conditions with highly nonpolar 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

**Scheme 3. Preparation of Lipophilic Ru–Alkylidene Complex 5**




carboxylic acid was next converted to the ester **25** derivative by treatment with 1-bromooctadecane (**26**) under basic conditions. Finally, coordination 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.

The CM activity of **5** was investigated using solvent-free conditions by studying the dimerization of 1-decene (**27**). The optimal catalyst loading was studied and compared with the commercially available catalyst **2** (Table 2). Initially, optimization studies were completed at room temperature (Table 2, entries 1–3). Catalyst **5** showed significantly higher



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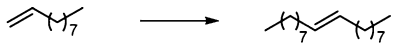
**Table 2. Optimization of CM Conditions Using 5[a]**



27 28

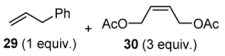
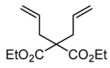
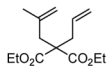
| entry | loading (mol %) | temp (°C) | catalyst **5**[a] | catalyst **2**[a] |
|---|---|---|---|---|
| 1 | 1.0 | 20 (rt) | 83% | 11% |
| 2 | 0.5 | 20 (rt) | 54% | 10% |
| 3 | 0.1 | 20 (rt) | 7% | 3% |
| 4 | 0.5 | 40 | 91% | – |
| 5 | 0.25 | 40 | 16% | – |
| 6 | 0.1 | 40 | 5% | – |

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

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 homogeneous reaction mixture. In contrast, catalyst **2** was largely insoluble in the neat substrate. By elevating the temperature to 40 °C, the catalyst loading could be further reduced (Table 2, entries 4–6). Optimal conditions were observed at 0.5 mol % **5** at 40 °C, providing 91% conversion to the dimerized product **28**.

With optimized conditions in hand, we studied the dimerization of other alkene substrates with catalyst **5** (Table 3). Self-metathesis of homologous terminal alkenes 1-octene

**Table 3. Selected Scope for Catalyst 5**

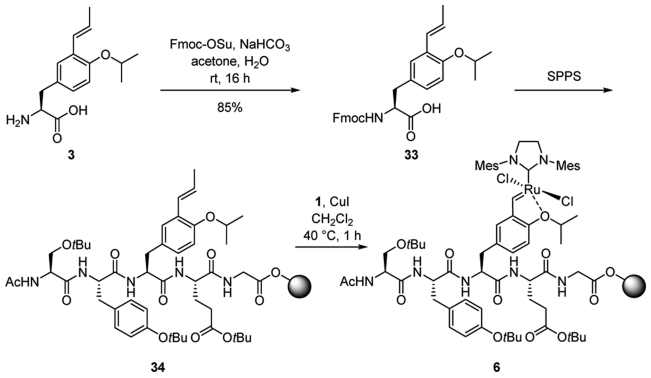
| entry | substrate | conv. (%)[a] |
|---|---|---|
| 1 | 1-octene | 95 |
| 2 | 1-hexene | >95 |
| 3 | ω-undecylenyl alcohol | >95 |
| 4 | 1-vinyl cyclohexanol | 90 |
| 5 |  **29** (1 equiv.) + **30** (3 equiv.) | 57[b] |
| 6 | 1,5-cyclooctadiene | 83 |
| 7 |  **31** | >95 |
| 8 |  **32** | 88 |

[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.

and 1-hexene provided excellent conversions to their respective cross-products (entries 1 and 2). High conversions were also observed for the CM of nonpolar alcohol *ω*-undecylenyl alcohol (entry 3) and 1-vinyl cyclohexanol (entry 4). CM 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 polymerization 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).

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. The reaction of **3** with Fmoc–OSu provided the required *N*-Fmoc analogue **33** (Scheme 4). SPPS began with Fmoc–Gly–

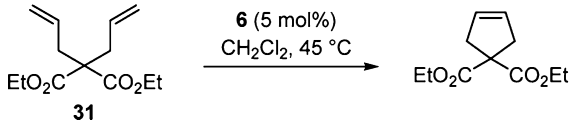
**Scheme 4. Preparation of Solid-Supported Olefin Ru–Alkylidene Complex 6**




Wang resin, and sequential coupling of Fmoc–Glu, *N*-Fmoc-protected analogue **33**, Fmoc–Tyr, and Fmoc–Ser delivered the solid-supported pentapeptide **34**. Subsequent coordination of **34** to catalyst **1** afforded the solid-supported Ru–alkylidene complex **6** as green resin beads.[13]

The catalytic activity of **6** was assessed with the RCM reaction of diethyl diallylmalonate **31** (Table 4, entry 1). At 5

**Table 4. RCM of 31 Catalyzed by a Single Batch of Resin-Bound Catalyst 6**




**31**

| run | time (h) | conversion[a] (%) | Ru[b] (ppm) |
|---|---|---|---|
| 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 was performed using ICP-MS.

mol % loading of **6**, the reaction proceeded to 95% after 0.5 h at 45 °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 colored (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



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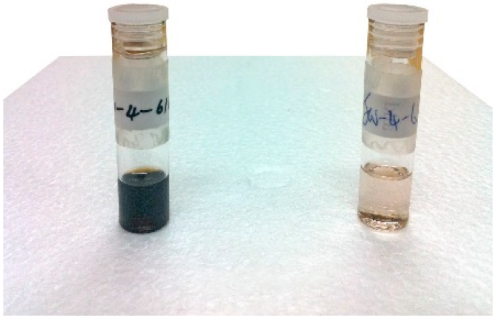

**Figure 2.** (left) RCM reaction of **31** using 5 mol % **2**; (right) RCM reaction of **31** using 5 mol % **6** (after filtration).

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]

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 inductively coupled plasma mass spectrometry (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 co-workers[10d] and Bannwarth and co-workers.[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 in five facile and high-yielding steps from commercially available Cbz-L-tyrosine (**7**). Further functionalization of **3** provides access to modified second-generation Hoveyda−Grubbs-type catalysts. Through this single synthetic approach, Ru−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 utilize this generic approach to access other tailored catalyst systems that 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, methanol ($CH_3OH$), copper(I) chloride (CuCl), Cbz-L-tyrosine, *o*-dichlorobenzene, dimethyl sulfoxide (DMSO), 2-iodopropane, potassium *tert*-butoxide ($KO^tBu$), stearic acid, and benzylidene [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium were used as supplied.

**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 colorless residue was resuspended in EtOAc (200 mL) and filtered, and the filtrate was concentrated under reduced pressure. The residue was then purified by silica chromatography (8:1, hexane/EtOAc) to give titled compound **8** as a colorless solid (11.7 g, 93%), mp 36.9−38.6 °C. IR: $\nu_{max}$ 3345m, 3067m, 3033m, 2937m, 1718s, 1611m, 1509s, 1455m, 1239s, 1219s, 1177s $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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 co-workers.[16] 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 colorless oil (7.78 g, 83%). IR: $\nu_{max}$ 3356brs, 3070m, 3032m, 2945m, 1696s, 1508s, 1438m, 1340m, 1260s, 1189s $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 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 co-workers.[16] 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) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica column chromatography (9:1, hexane/EtOAc) to give titled compound **10** as a colorless oil (6.75 g, 80%). IR: $\nu_{max}$ 3338brs, 3067m, 2976m, 2936m, 1719s, 1496s, 1454m, 1382m, 1339m, 1246s, 1189m $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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 × 50 mL). The



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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 °C 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%), mp 187.4−189.1 °C. IR: $\nu_{max}$ 3448brs, 3200brs, 3038s, 2975s, 2933m, 2913m, 1605s, 1586s, 1489s, 1437m, 1397s, 1332s, 1242s, 1110s, 954s cm$^{-1}$. $^1$H NMR (400 MHz, MeOD): $\delta$ 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{$^1$H} NMR (100 MHz, MeOD): $\delta$ 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 × 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: $\nu_{max}$ 2912s, 2874s, 1735m, 1638w, 1580m, 1491m, 1347m, 1243m, 1201m, 1094s cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 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 × 50 mL). The combined organic extracts were washed with 10% (w/v) aqueous $CuSO_4$ (2 × 50 mL), $H_2O$ (1 × 50 mL), and brine (1 × 50 mL), 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 colorless oil. IR: $\nu_{max}$ 2873brs, 1741m, 1662m, 1582m, 1490m, 1450w, 1490m, 1350m, 1243m, 1095s cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 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: $\nu_{max}$ 3339w, 2872s, 1739m, 1655m, 1581m, 1485s, 1449m, 1421m, 1256m, 1095s, 1029s cm$^{-1}$. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 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{$^1$H} NMR (150 MHz, $CD_3OD$): $\delta$ 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.** 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 homogeneous mixture was stirred at 40 °C for 16 h. The reaction mixture was concentrated in vacuo, dissolved in $D_2O$, and analyzed by $^1$H 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 (3 mL) 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 × 50 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give amide **24** that 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 × 50 mL). The combined organic extracts were washed with $H_2O$ (2 × 50 mL) and brine (1 × 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 colorless solid (206 mg, 69%), mp 69.2−72.5 °C. IR: $\nu_{max}$ 3254w, 2914s, 2849s, 1736m, 1638m, 1542m, 1491m, 1467m, 1372w, 1244s, 1112m, 967m cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 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{$^1$H} NMR (75 MHz, $CDCl_3$): $\delta$ 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,


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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%), mp 120.6−127.8 °C. IR: $\nu_{max}$ 3320w, 2920s, 2851s, 1736m, 1672m, 1518m, 1487m, 1420m, 1262s, 1221m, 1198m, 1133m, 1105m cm$^{-1}$. $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ 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{$^1$H} NMR (150 MHz, $C_6D_6$): $\delta$ 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.** 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 analyzed by $^1$H 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 $\mu$mol) 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 $\mu$mol) 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 the organic phase was 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 colorless solid (315 mg, 85%). IR: $\nu_{max}$ 3294m, 3067w, 2984w, 2850w, 1691s, 1543m, 1490m, 1430m, 1297m, 1247s, 735s cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 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 of amino acid, 0.05 mmol of HATU, 0.10 mmol of NMM, 3 mL of 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 were washed (3 × 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 catalyst **6** from the reaction was achieved via canula filtration. The solid-supported catalyst was washed further with $CH_2Cl_2$ (2 × 5 mL) and dried in vacuo. The resultant filtrate was concentrated in vacuo, dissolved in $CDCl_3$, and analyzed by $^1$H NMR spectroscopy. The filtrate was diluted in MQ $H_2O$ (100 mL), and the Ru content was analyzed by ICP-MS.

## ■ ASSOCIATED CONTENT

### Supporting Information

General experimental information; $^1$H and $^{13}$C{$^1$H} NMR spectra of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01091.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: andrea.robinson@monash.edu.


### Notes

The authors declare no competing financial interest

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(12) Grubbs and co-workers[8g] generate a water-soluble Ru-alkylidene catalyst using longer PEG motifs ($M_n \sim 2639$). 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 equiv of **1** to ligand **34**. RCM of **31** using 5 mol % Ru was conducted and showed a decline in catalyst activity and recyclability.

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