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PQS-2: ring-closing- and cross-metathesis reactions on lipophilic substrates; in water only at room temperature, with in-flask catalyst recycling

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ABSTRACT

A ubiquinol side-chain hydrogenated version (PQS-2) of the recently introduced PQS is described. It forms catalytic nanomicellar reactors in water that provide the medium for highly reactive Ru carbene catalysts to effect both ring closing metathesis to trisubstituted olefins and cross-metathesis reactions at room temperature. The catalyst can be recycled without removal from the reaction vessel.

1. Introduction

In a recent report we disclosed a new platform for catalysis, 'PQS', a nanomicelle-forming amphiphile that provides a synthetic handle in the form of its available OH group to which a variety of otherwise water-insoluble species can be covalently attached (Fig. 1).[1] This 'designer' surfactant falls within the guidelines put forth by Anastas in the '12 Principles of Green Chemistry', being 'benign by design'.[2] That is, PQS is composed of three components: (1) the dietary supplement ubiquinol (i.e., reduced coenzyme Q_{10})[3]; (2) sebacic acid, and (3) a polyethyleneglycol (PEG-2000), all totally safe for human consumption. Moreover, it's derivatives containing covalently bound catalysts would possess all of the elements outlined by Sheldon and co-workers for a water-soluble, environmentally innocuous, and recyclable species.[4] Initially developed derivative **1** features the Grubbs–Hoveyda first generation catalyst (Fig. 2),[5] conceived as a 'proof of principle' albeit potentially quite useful example. It was applied to ring-closing metathesis (RCM) reactions en route to disubstituted cycloalkenes.[1] To further apply this technology toward more substituted cyclic arrays, and/or potentially products of cross-metathesis (CM),[6] the alternative species possessing the Grubbs–Hoveyda second generation ruthenium catalyst (GH-2)[7] would be needed. In this report we outline a synthesis of the side-chain saturated analog **2**, along with its use in both RCM and CM reactions, in water at room temperature.

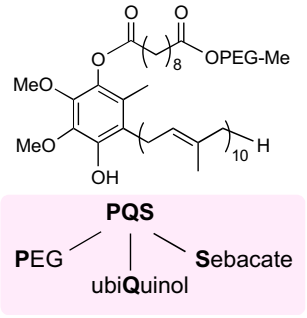

Figure 1. Components of PQS.

2. Results and discussion

The route to the more reactive *N*-heterocyclic (NHC)-ligated ruthenium catalyst **2** at first was envisioned to go through the identical precursor[1] used to arrive at the less reactive analog **1**. However, since Grubbs-2 carbenes metathesize trisubstituted olefins,[8] and given its forced presence within the micellar core, undesired interactions with the olefins that constitute the parent ubiquinol side-chain would be anticipated; and this is precisely what occurs upon dissolution of the side-chain unsaturated analog of **2** in water.

A simple solution was to reduce PQS by catalytic hydrogenation over Pd/C in methanol at 22 °C, producing the saturated hydroquinone monoester **3** ('PQS-2') (Scheme 1). Alternatively, PQS-2 could be prepared from ubiquinol or directly from CoQ_{10} by the same hydrogenation, which reduces both the *p*-quinone and/or side-chain, simultaneously (Scheme 2). Mono-esterification of hydroquinone **4** with excess sebacoyl chloride followed by introduction of M-PEG-2000 afforded the saturated derivative **3** (PQS-2). Diester **3** is freely soluble in pure water, and spontaneously forms 19 nm micelles.[9]

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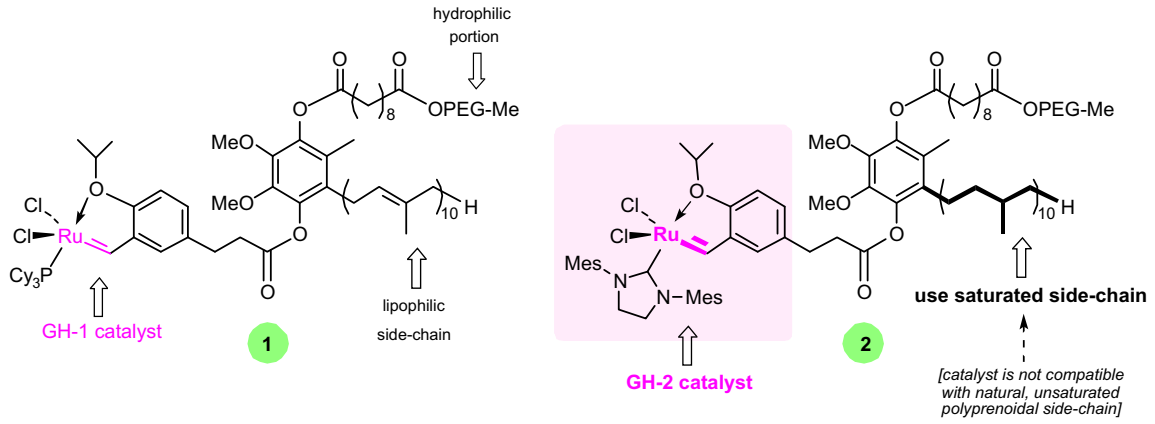
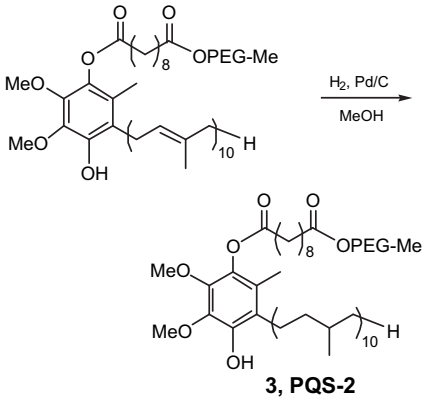
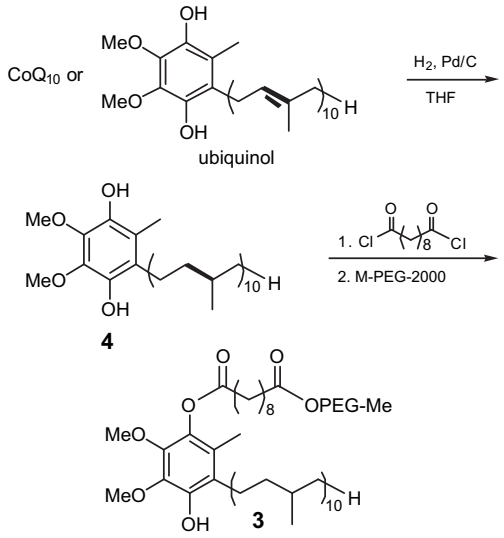


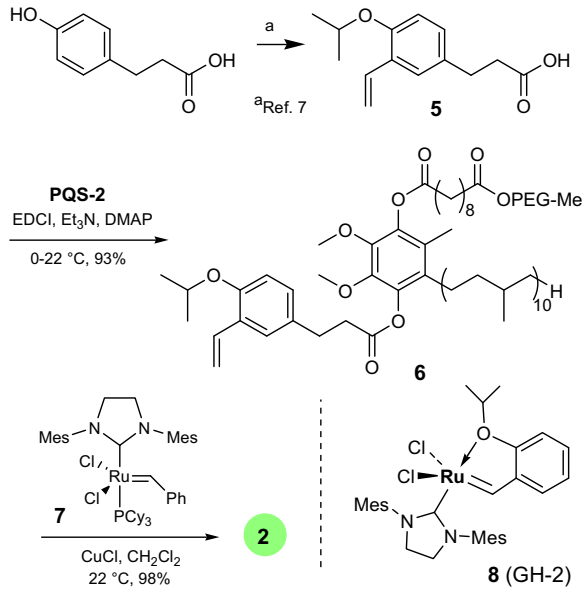
Figure 2. PQS-attached Grubbs–Hoveyda metathesis catalysts **1** and **2**.



Scheme 1. Preparation of PQS-2 (**3**).



Scheme 2. Alternative route to preparation of PQS-2 (**3**).



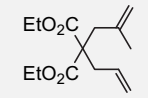
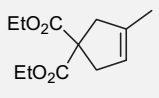
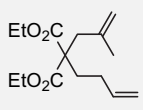
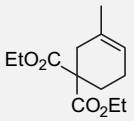
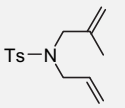
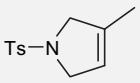
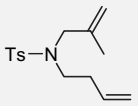
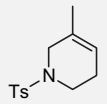
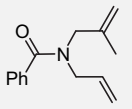
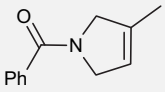
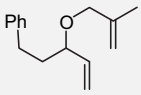
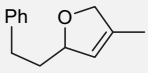
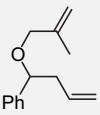
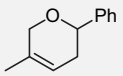
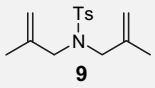
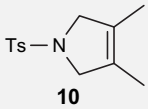
Scheme 3. Preparation of PQS-2-attached GH-2 catalyst **2**.

Treatment of PQS-2 (**3**) with acid **5** led to carbene precursor **6** (Scheme 3). Exposure of **6** to the Grubbs-2 Ru carbene **7**[10] under standard conditions of phosphine-sequestering CuCl in CH_2Cl_2 led in high yield to the stable and solid catalyst **2**, the water-soluble analog of **8**.[11]

Ring-closing metathesis reactions of dienes composed of both a mono- and 1,1-disubstituted olefin could be smoothly effected in water containing only 2% catalyst **2** (by weight) at room temperature. Representative trisubstituted olefinic products are shown in Table 1. Each was completed within a three-hour time frame at a global concentration of 0.1 M. No attempt was made to exclude air from these cyclizations. Carbocycles (5- and 6-membered rings; entries 1, 2), as well as nitrogen- and oxygen-containing heterocycles, were readily formed in good isolated yields (entries 3–5, and entries 6 and 7, respectively). The unique case of diene **9** (entry 8) required more forcing conditions of 60 °C for 24 h to arrive at the tetra-substituted olefin, 3,4-dimethylated-3-pyrroline, **10**.

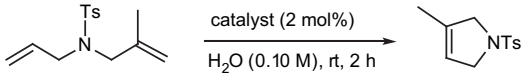
Recycling of catalyst **2** was straightforward: Et_2O is added to the reaction flask (open to air), the mixture is stirred briefly, after which the organic solvent (repeated two times) is removed/recovered leading to the desired product. The aqueous phase retaining catalyst **2** was reused simply by addition of fresh substrate. As indicated in Table 2 below, after eight recycles, the extent of conversion was still ≥90%, using the arbitrarily selected conditions (3 h). The drop in activity after what amounts to ca. two total days of handling is innate to the ruthenium

Table 1
RCM reactions in water only, catalyzed by catalyst **2**[a]

Entry	Substrate	Product	Yield[b] (%)
1			93
2			85
3			99
4			95
5			98
6			98
7			99
8	 **9**	 **10**	70[c]

[a] 2 mol % catalyst **2** at 0.1 M at 22 °C for 3 h.
[b] Isolated yield of chromatographically pure materials.
[c] 5 mol % catalyst at 60 °C for 24 h.

Table 2
Recycling of catalyst **2** in RCM reactions[a]



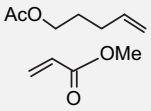
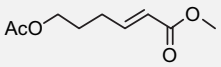
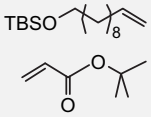
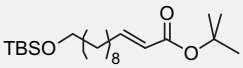
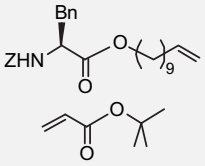
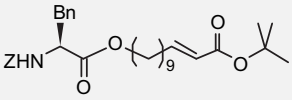
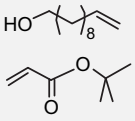
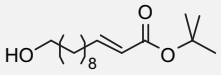
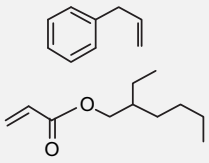
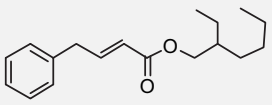
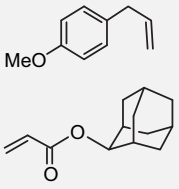
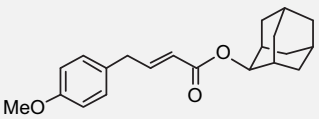
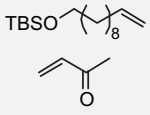
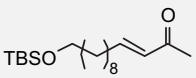
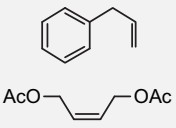
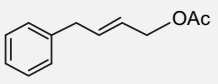
Catalyst	Cycle (% conversion)[b]							
	1	2	3	4	5	6	7	8
Catalyst **2**	>99	>99	98	97	95	94	92	90
Grubbs-2 (**7**)	85	9						
GH-2 (**8**)	80	<1						

[a] The reactions were performed with 0.1 mmol substrate.
[b] Determined by ^{1}H NMR spectroscopy at 400 MHz.

complex in **2**, and not due to loss of catalyst in handling (vide infra).

Cross-metathesis reactions can also be catalyzed by the GH-2 analog **2** in water (0.5 M) at room temperature, due to its enhanced activity relative to that of our first generation catalyst (i.e., PQS-1, **1**).[1] Table 3 illustrates several examples, these results being similar to

Table 3
CM reactions in water only, catalyzed by catalyst **2**[a]

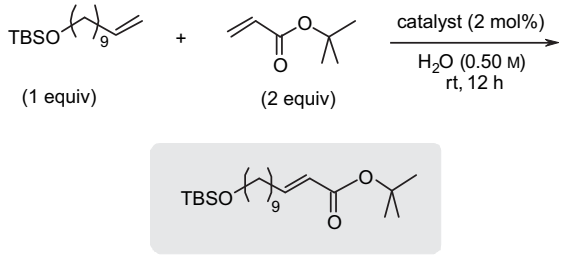
Entry	Partners	Product; % yield[b] (ratio)[c]
1		 82 (>20:1)
2		 94 (*E* only)
3		 97 (*E* only)
4		 85 (>20:1)
5		 94 (9:1)
6		 73 (*E* only)
7		 80 (*E* only)
8		 84 (13:1)

[a] 2 mol % catalyst **2** at 0.5 M at 22 °C for 12 h.
[b] Isolated yield of chromatographically pure materials.
[c] *E*/*Z* ratio determined by ^{1}H NMR.

those seen previously using the designer surfactant 'PTS' under related green conditions with commercially available Grubbs-2 catalyst.[12] Acrylates of varying levels of lipophilicity (methyl; entry 1, *t*-butyl, entries 2–4; 2-ethylhexyl, entry 5) all participated to afford high-to-exclusively *E*-olefinic products, while MVK (entry 7) led to only *E*-enone, and a 1,4-diacetate (entry 8) readily provided the corresponding allylic acetate.

As with RCM reactions highlighted above, processing allows for recycling without catalyst removal from the reaction vessel. Table 4 documents that PQS-2 at the 2 mol % level in water can mediate the anticipated cross-couplings, although each intermolecular coupling

Table 4
Recycling of catalyst **2** in olefin CM reactions[a]



	Cycle(% conversion)[b]						
Catalyst	1	2	3	4	5	6	7
Catalyst **2**	>99	97	92	86 (94)[c]	78 (88)	70 (82)	65 (93)[c]
Grubbs-2 (**7**)	70	<1					
GH-2 (**8**)	56	<1					

[a] The reactions were performed with 0.25 mmol substrate.
[b] Determined by ^{1}H NMR spectroscopy at 400 MHz.
[c] Catalyst **2** (1.5 mol %) was added again.

takes at least four times longer than related intramolecular (RCM) reactions (i.e., 12 vs 3 h). Hence, the apparent innate instability of the GH-2 catalyst in water over time (several days) leads to gradually reduced levels of conversion, again under the chosen 12 h time frame; longer reaction times would increase these levels. That the catalyst is losing activity can be shown by addition of fresh PQS-2 after every three recycles: the conversions return just about to the earlier levels seen.

3. Conclusions

In summary, a new catalyst system has been developed that, as stated by Sheldon, Arends, and Hanefeld,[4] by design "eliminates waste at source"; it prevents pollution by minimizing the amount of water needed as the medium, and eliminates reliance on any organic solvent for RCM and CM reactions. Workup has been streamlined so as to allow in-flask processing with minimal use of a single organic solvent that can subsequently be recovered. No special precautions or handling requirements are needed, nor is any additional energetic input involved; indeed, these reactions are done in air, in water, and at room temperature.

4. Experimental

4.1. General

All reactions were preformed in Biotage 2–5 mL microwave reactor vials containing a Teflon-coated stir bar. Column chromatography was preformed using Silicycle Silia-P 60 Å flash silica gel. Thin-Layer-Chromatography analysis was conducted using commercially available EMD silica gel 60 F_{254} plates. Nuclear Magnetic Resonance spectra were obtained on a Varian Inova system, in $CDCl_3$, with proton and carbon resonances at 400 and 100 MHz, respectively, and are referenced to the residual solvent signal at δ 7.27 ppm for ^{1}H and δ 77.23 ppm for ^{13}C. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, sep=septet), coupling constant and integration. Data for ^{13}C NMR are reported in terms of chemical shift. Infrared spectra were obtained either, neat or by thin-film, on NaCl plates using a JASCO FT/IR-430 series spectrometer and are reported as cm^{-1}. Mass spectral data were acquired on either a VF Autospec or an analytical VG-70-250 HF spectrometer. Solvents and reagents were all obtained from commercial vendors and used with no further purification.

4.2. Compound 3 (PQS-2)

A well-stirred suspension of PQS[1] (0.60 g, 0.20 mmol) and Pd/C (10% w/w, 78 mg) in dry MeOH (5 mL) was fitted to a source of hydrogen (1 atm) and stirred at 22 °C for 12 h. The mixture was filtered through a pad of Celite and washed with MeOH. The combined filtrates were concentrated in vacuo affording a colorless liquid, which was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2 to 5% MeOH/CH_2Cl_2 gradient afforded the title compound **3** (0.57 g, 95%, 2:1 mixture of two regioisomers) as a white foam. IR (film): 3496, 2924, 2888, 1758, 1736, 1467, 1376, 1360, 1344, 1280, 1242, 1146, 1114, 1062, 963, 948, 843 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (s, 0.35H), 5.66 (s, 0.65H), 4.24–4.21 (m, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.70–3.45 (m, PEG), 3.38 (s, 3H), 2.60–2.54 (m, 2H), 2.33 (t, J=7.6 Hz, 2H), 2.16 (s, 1.05H), 2.02 (s, 1.95H), 1.79–1.72 (m, 2H), 1.65–1.59 (m, 2H), 1.55–1.49 (m, 2H), 1.38–1.04 (m, 74H), 0.96–0.83 (m, 33H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 172.4, 172.1, 145.3, 144.8, 141.8, 137.6, 135.1, 124.3, 123.1, 117.3, 71.9, 70.5–70.1 (m, PEG), 69.2, 63.3, 60.9, 60.8, 60.5, 60.4, 59.0, 39.3, 37.44, 37.38, 37.34, 37.29, 37.23, 37.13, 36.4, 36.3, 34.1, 34.0, 33.9, 33.3, 32.7, 29.7, 29.1, 27.9, 25.1, 24.8, 24.7, 24.4, 24.1, 22.7, 22.6, 19.8, 19.75, 19.69, 19.6, 11.8, 11.2; MS (ESI): $m/3z$ ~1044 $(M+3Na)^{+3}$.

4.3. Compound 6 (precursor to catalyst 2)

Diester **3** (0.63 g, 0.21 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. 1-(*p*-Isopropoxy-*m*-vinylphenyl)propionic acid[7] (**5**) (0.063 g, 0.27 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC) (0.06 g, 0.31 mmol), and DMAP (0.01 g, 0.08 mmol) were then directly added in succession to the mixture as solids. Et_3N (0.05 mL, 0.36 mmol) was added through a syringe. The resulting mixture was stirred at 22 °C for 20 h. Water was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, water, brine, dried and concentrated in vacuo affording a colorless liquid, which was purified by flash column chromatography on silica gel, eluting with Et_2O, followed by CH_2Cl_2 to 6% MeOH/CH_2Cl_2 gradient afforded the title compound **6** (0.63 g, 93%, 2:1 mixture of two regioisomers) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.36 (m, 1H), 7.10–7.07 (m, 1H), 7.02 (dd, J=17.6, 11.2 Hz, 1H), 6.82–6.79 (m, 1H), 5.74–5.69 (m, 1H), 5.22–5.19 (m, 1H), 4.48 (sep, J=6.0 Hz, 1H), 4.21–4.19 (m, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.69–3.43 (m, PEG), 3.36 (s, 3H), 3.04–3.00 (m, 2H), 2.92–2.86 (m, 2H), 2.60–2.54 (m, 2H), 2.33–2.29 (m, 2H), 2.02 (s, 1.95H), 1.94 (s, 1.05H), 1.79–1.74 (m, 2H), 1.63–1.57 (m, 2H), 1.53–1.46 (m, 2H), 1.41–1.04 (m, 80H), 0.93–0.84 (m, 33H); MS (ESI): $m/3z$ ~1117 $(M+3Na)^{+3}$.

4.4. Catalyst 2

Styrene **6** (0.58 g, 0.18 mmol) was weighed into a 50 mL round-bottom flask and dissolved in 9 mL of CH_2Cl_2. (4,5-DihydroIMES)$(PCy_3)Cl_2$Ru=CHPh (**7**) (0.19 g, 0.22 mmol) and CuCl (0.024 g, 0.24 mmol) were added directly to this solution as solids. The mixture was stirred for a period of 4 h at 22 °C, during which time the original purple solution turned a dark green/brown color. The following workup procedures were conducted in air with reagent grade solvents. The mixture was concentrated at reduced pressure and passed through a short column of silica gel eluting with CH_2Cl_2 followed by Et_2O. Finally, the column was flushed with 6% MeOH/CH_2Cl_2, at which point the product elutes (green band). Solvent removal afforded the title compound **2** (0.65 g, 98%, 2:1 mixture of two regioisomers) as a dark green foam. IR (neat): 2925, 2869, 1763, 1736, 1461, 1421, 1377, 1351, 1295, 1254, 1108, 949, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):

δ 16.53 (s, 1H), 7.42–7.39 (m, 1H), 7.06 (s, 4H), 6.81 (d, *J*=1.6 Hz, 1H), 6.73 (d, *J*=8.0 Hz, 1H), 4.87 (sep, *J*=6.4 Hz, 1H), 4.22 (t, *J*=4.8 Hz, 2H), 4.17 (s, 4H), 3.79 (s, 3H), 3.71 (s, 3H), 3.70–3.45 (m, PEG), 3.38 (s, 3H), 3.09–3.05 (m, 2H), 2.87–2.80 (m, 2H), 2.62–2.56 (m, 2H), 2.47 (br s, 12H), 2.40 (s, 6H), 2.33 (t, *J*=7.2 Hz, 2H), 2.06 (s, 2.05H), 1.98 (s, 1.05H), 1.80–1.76 (m, 2H), 1.64–1.60 (m, 2H), 1.55–1.46 (m, 2H), 1.35–1.06 (m, 80H), 0.93–0.83 (m, 33H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.5, 172.72, 172.68, 170.9, 170.6, 170.0, 169.8, 150.2, 144.5, 142.54, 142.51, 140.1, 139.9, 139.6, 139.4, 137.9, 133.2, 128.9, 128.6, 128.5, 123.6, 123.4, 121.7, 112.2, 74.2, 71.2, 69.8–69.4 (m, PEG), 68.4, 62.6, 59.8, 59.7, 58.3, 38.7, 36.8, 36.7, 36.6, 36.4, 35.8, 35.0, 33.4, 33.2, 32.6, 32.5, 32.1, 32.04, 32.0, 28.8, 28.4, 28.3, 27.3, 26.3, 25.7, 25.5, 24.4, 24.2, 24.1, 23.7, 22.2, 22.0, 20.42, 20.36, 19.2, 19.16, 19.1, 19.0, 18.9, 11.3; MS (ESI): *m*/3*z* ~1271 $(M+3Na)^{+3}$.

4.5. General procedure for ring-closing metathesis

Diene (0.10 mmol) and catalyst **2** (7.5 mg, 0.002 mmol) were both added into a Teflon-coated-stir-bar-containing Biotage 2–5 mL microwave reactor vial at room temperature, and sealed with a septum. H_2O (1.0 mL; all RCM reaction were conducted at 0.1 M unless stated otherwise) was added, via syringe, and the resulting solution was allowed to stir at room temperature for 3 h. The homogeneous reaction mixture was then diluted with EtOAc (2 mL), filtered through a bed of silica gel layered over Celite, and the bed further washed (2×4 mL) with EtOAc to collect all of the cyclized material. The volatiles were removed in vacuo to afford the crude product, which was subsequently purified by flash chromatography using silica gel (solvent noted) to afford the title compounds.

4.5.1. Diethyl 3-methylcyclopent-3-ene-1,1-dicarboxylate (Table 1, Entry 1). The representative procedure was followed using diethyl 2-allyl-2-(2-methylallyl)malonate[13] (25.5 mg, 0.10 mmol) and catalyst **2** (8.0 mg, 0.002 mmol). Column chromatography on silica gel (eluting with 16% EtOAc/hexanes) afforded the product as a colorless oil (21 mg, 93%). The ^{1}H NMR spectral data obtained was in accord with data previously reported for this compound.[14]

4.5.2. Diethyl 3-methylcyclohex-3-ene-1,1-dicarboxylate (Table 1, Entry 2). The representative procedure was followed using diethyl 2-(but-3-enyl)-2-(2-methylallyl)malonate (27 mg, 0.10 mmol) and catalyst **2** (8.0 mg, 0.002 mmol). Column chromatography on silica gel (eluting with 2% EtOAc/hexanes) afforded the product as a colorless oil (20.5 mg, 85%). IR (neat): 2979, 2936, 2851, 1735, 1445, 1388, 1366, 1339, 1314, 1286, 1252, 1176, 1079, 1046, 1022, 968, 913 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (br s, 1H), 4.18 (q, *J*=7.2 Hz, 4H), 2.43 (s, 2H), 2.09–2.07 (m, 4H), 1.70 (s, 3H), 1.25 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 131.5, 120.1, 61.4, 53.8, 35.2, 27.3, 23.7, 22.6, 14.3; MS (EI) *m*/*z* (%): 240 (15), 195 (9), 166 (44), 137 (18), 93 (100); HRMS (EI) calcd for $C_{13}H_{20}O_4$ $[M]^+$=240.1362, found 240.1361.

4.5.3. 3-Methyl-N-tosyl-2,5-dihydro-1H-pyrrole (Table 1, Entry 3). The representative procedure was followed using *N*-allyl-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (27 mg, 0.10 mmol) and catalyst **2** (8.0 mg, 0.002 mmol). Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a white solid (24 mg, 99%). The ^{1}H NMR spectral data obtained was in accord with data previously reported for this compound.[15]

4.5.4. 5-Methyl-N-tosyl-1,2,3,6-tetrahydropyridine (Table 1, Entry 4). The representative procedure was followed using *N*-(but-3-enyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (28 mg, 0.10 mmol) and catalyst **2** (8.0 mg, 0.002 mmol). Column chromatography on silica gel (eluting with 6% EtOAc/hexanes) afforded the product as a white solid (24 mg, 95%). The ^{1}H NMR spectral data obtained was in accord with data previously reported for this compound.[16]

4.5.5. (3-Methylcyclopent-3-enyl)(phenyl)methanone (Table 1, Entry 5). The representative procedure was followed using *N*-allyl-*N*-(2-methylallyl)benzamide[13] (21.5 mg, 0.10 mmol) and catalyst **2** (8.0 mg, 0.002 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product as a colorless oil (18.5 mg, 99%). The ^{1}H NMR spectral data obtained was in accord with data previously reported for this compound.[13]

4.5.6. 4-Methyl-2-phenethyl-2,5-dihydrofuran (Table 1, Entry 6). The representative procedure was followed using (3-(2-methylallyloxy)pent-4-enyl)benzene (22 mg, 0.10 mmol) and catalyst **2** (8.0 mg, 0.002 mmol). Column chromatography on silica gel (eluting with 2% EtOAc/hexanes) afforded the product as a colorless oil (19 mg, 98%). IR (neat): 3062, 3027, 2918, 2858, 1668, 1604, 1496, 1454, 1366, 1268, 1194, 1061, 1031, 992, 972, 936 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, *J*=7.2 Hz, 2H), 7.22–7.17 (m, 3H), 5.40 (br s, 1H), 4.85 (br s, 1H), 4.58–4.47 (m, 2H), 2.78–2.63 (m, 2H), 1.89–1.80 (m, 2H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5, 136.5, 128.6, 128.4, 125.8, 123.6, 86.2, 77.9, 38.2, 31.7, 12.5; MS (EI) *m*/*z* (%): 188 (8), 110 (7), 91 (24), 83 (100); HRMS (EI) calcd for $C_{13}H_{16}O$ $[M]^+$=188.1201, found 188.1209.

4.5.7. 5-Methyl-2-phenyl-3,6-dihydro-2H-pyran (Table 1, Entry 7). The representative procedure was followed using (1-(2-methylallyloxy)but-3-enyl)benzene (20 mg, 0.10 mmol) and catalyst **2** (8.0 mg, 0.002 mmol). Column chromatography on silica gel (eluting with 2% EtOAc/hexanes) afforded the product as a colorless oil (17 mg, 99%). The ^{1}H NMR spectral data obtained was in accord with data previously reported for this compound.[17]

4.5.8. 3,4-Dimethyl-N-tosyl-2,5-dihydro-1H-pyrrole (Table 1, Entry 8). The representative procedure was followed using 4-methyl-*N*,*N*′-bis(2-methylallyl)benzenesulfonamide (21 mg, 0.075 mmol) and catalyst **2** (15 mg, 0.0038 mmol). Resulting solution was allowed to stir at 60 °C for 24 h. Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a white solid (13 mg, 70%). The ^{1}H NMR spectral data obtained was in accord with data previously reported for this compound.[18]

4.6. Diethyl 2-(but-3-enyl)-2-(2-methylallyl)malonate

To a solution of sodium ethoxide (0.11 g, 1.62 mmol) in EtOH (5 mL) was added diethyl 2-(2-methylallyl)malonate[19] (0.30 g, 1.40 mmol). After 15 min, 4-bromo-1-butene (0.21 mL, 2.10 mmol) was added and stirred at 22 °C for 24 h. Then the reaction mixture was quenched with water and extracted with Et_2O. The combined organic layer was washed with water, dried, and concentrated in vacuo gave yellow liquid, which was subsequently purified by flash chromatography using silica gel (5% EtOAc/hexanes) to afford the title compound (0.19 g, 50%) as a colorless liquid. IR (neat): 3078, 2980, 2938, 2873, 1733, 1643, 1448, 1367, 1298, 1264, 1182, 1095, 1035, 995, 900, 864 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3): δ 5.83–5.73 (m, 1H), 5.02 (dd, *J*=17.2, 1.6 Hz, 1H), 4.96 (dd, *J*=10.4, 1.6 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 4.21–4.16 (m, 4H), 2.73 (s, 2H), 1.98 (s, 4H), 1.66 (s, 3H), 1.26 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 140.9, 137.8, 115.7, 115.1, 61.4, 56.9, 40.3, 31.6, 28.7, 23.4, 14.2; MS (ESI): *m*/*z* 291 (M+Na), 269 (M+H); HRMS (ESI) calcd for $C_{15}H_{24}O_4Na$ $[M+Na]^+$=291.1572, found 291.1571.

4.7. 1-(3-(2-Methylallyloxy)pent-4-enyl)benzene

A solution of 5-phenylpent-1-en-3-ol[20] (0.11 g, 0.68 mmol) in THF (3 mL) was added to a stirred suspension of NaH (0.06 g,

1.50 mmol, 60% suspension in mineral oil) in THF (3 mL) at 0 °C. After H_2 evolution ceased, the mixture was stirred at 22 °C for 30 min. To this mixture methallyl bromide (0.10 mL, 0.99 mmol) was added dropwise via syringe at 0 °C and the solution was allowed to warm to room temperature and stirred for 6 h. Then the reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layer was washed with water, dried, and concentrated in vacuo gave yellow liquid, which was subsequently purified by flash chromatography using silica gel (2% EtOAc/hexanes) to afford the title compound (0.14 g, 98%) as a colorless liquid. IR (neat): 3077, 3027, 2978, 2919, 2858, 1656, 1604, 1496, 1454, 1373, 1322, 1180, 1095, 993, 926, 899 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.29 (m, 2H), 7.24–7.20 (m, 3H), 5.76 (ddd, J=18.0, 10.4, 7.6 Hz, 1H), 5.27–5.20 (m, 2H), 5.03–5.02 (m, 1H), 4.93–4.92 (m, 1H), 3.99 (d, J=12.4 Hz, 1H), 3.78 (d, J=12.4 Hz, 1H), 3.73 (q, J=7.6 Hz, 1H), 2.83–2.68 (m, 2H), 2.05–1.96 (m, 1H), 1.89–1.81 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 142.3, 139.1, 128.6, 128.5, 125.9, 117.4, 112.0, 79.9, 72.2, 37.3, 31.8, 19.9; MS (ESI): m/z 239 (M+Na), 217 (M+H).

4.8. General procedure for cross metathesis

Alkene (0.25 mmol), acrylate (0.50 mmol) and catalyst **2** (19 mg, 0.005 mmol) were sequentially added into a Teflon-coated-stir-bar-containing Biotage 2–5 mL microwave reactor vial at room temperature, and sealed with a septum. H_2O (0.5 mL; all cross-coupling reactions were conducted at 0.5 M unless stated otherwise) was added, via syringe, and the resulting solution was allowed to stir at room temperature for 12 h. The homogeneous reaction mixture was then diluted with EtOAc (5 mL), filtered through a bed of silica gel layered over Celite, and the bed further washed (3×10 mL) with EtOAc to collect all of the cross-coupled material. The volatiles were removed in vacuo to afford the crude product, which was subsequently purified by flash chromatography on silica gel (solvent noted) to afford the title compounds.

4.8.1. (E)-Methyl 6-acetoxy-2-hexenoate (Table 3, Entry 1). The representative procedure was followed using pent-4-enyl acetate (32 mg, 0.25 mmol), methyl acrylate (65 mg, 0.75 mmol) and catalyst **2** (19 mg, 0.005 mmol). Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a colorless oil (38 mg, 82%). The spectroscopic data obtained for the product was in accord with those previously reported for this compound.[12]

4.8.2. (E)-tert-Butyl 12-(tert-butyldimethylsilyloxy)-2-dodecenoate (Table 3, Entry 2). The representative procedure was followed using *tert*-butyldimethyl(undec-10-enyloxy)silane[21] (71 mg, 0.25 mmol), *tert*-butyl acrylate (64 mg, 0.50 mmol) and catalyst **2** (19 mg, 0.005 mmol). Column chromatography on silica gel (eluting with 2% EtOAc/hexanes) afforded the product as a colorless oil (90 mg, 94%). IR (neat): 2928, 2856, 1715, 1654, 1463, 1390, 1366, 1289, 1254, 1217, 1157, 1099, 1006, 982, 938, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (dt, J=15.6, 7.2 Hz, 1H), 5.74 (dt, J=15.6, 1.6 Hz, 1H), 3.60 (t, J=6.8 Hz, 2H), 2.16 (qd, J=6.8, 1.6 Hz, 2H), 1.55–1.50 (m, 2H), 1.49 (s, 9H), 1.46–1.40 (m, 2H), 1.33–1.28 (m, 10H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 148.3, 123.1, 80.1, 63.5, 33.0, 32.2, 29.7, 29.6, 29.5, 29.3, 28.33, 28.26, 26.2, 26.0, 18.5, −5.1; MS (ESI): m/z 423 (M+K), 407 (M+Na), 385 (M+H); HRMS (ESI) calcd for $C_{22}H_{44}O_3SiNa$ $[M+Na]^+$=407.2957, found 407.2965.

4.8.3. (R,E)-tert-butyl 12-(2-(benzyloxycarbonylamino)-3-phenylpropanoyloxy)dodec-2-enoate (Table 3, Entry 3). The representative procedure was followed using (*R*)-undec-10-enyl 2-(benzyloxycarbonylamino)-3-phenylpropanoate (113 mg, 0.25 mmol), *tert*-butyl acrylate (64 mg, 0.50 mmol) and catalyst **2** (19 mg, 0.005 mmol). Column chromatography on silica gel (eluting with 6% EtOAc/hexanes) afforded the product as a colorless oil (134 mg, 97%). The spectroscopic data obtained for the product were in accord with that previously reported for this compound.[12]

4.8.4. (E)-tert-Butyl 11-hydroxy-2-undecenoate (Table 3, Entry 4). The representative procedure was followed using 10-undecenol (43 mg, 0.25 mmol), *tert*-butyl acrylate (64 mg, 0.50 mmol) and catalyst **2** (19 mg, 0.005 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product as a colorless oil (58 mg, 85%). The spectroscopic data obtained for the product were in accord with that previously reported for this compound.[12]

4.8.5. (E)-2-Ethylhexyl 4-phenyl-2-butenoate (Table 3, Entry 5). The representative procedure was followed using allylbenzene (30 mg, 0.25 mmol), 2-ethylhexyl acrylate (92 mg, 0.50 mmol) and catalyst **2** (19 mg, 0.005 mmol). Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a colorless oil (65 mg, 94%). The spectroscopic data obtained for the product were in accord with that previously reported for this compound.[12]

4.8.6. (E)-2-Adamantyl 4-(4-methoxyphenyl)-2-butenoate (Table 3, Entry 6). The representative procedure was followed using 4-allylanisole (37 mg, 0.25 mmol), 2-adamantyl acrylate (103 mg, 0.50 mmol) and catalyst **2** (19 mg, 0.005 mmol). Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a colorless oil (59 mg, 73%). The spectroscopic data obtained for the product were in accord with that previously reported for this compound.[12]

4.8.7. (E)-13-(tert-Butyldimethylsilyloxy)tridec-3-en-2-one (Table 3, Entry 7). The representative procedure was followed using *tert*-butyldimethyl(undec-10-enyloxy)silane[21] (72 mg, 0.25 mmol), methyl vinyl ketone (54 mg, 0.77 mmol) and catalyst **2** (19 mg, 0.005 mmol). Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless oil (66 mg, 80%). IR (neat): 2936, 2855, 1700, 1677, 1629, 1464, 1433, 1388, 1361, 1253, 1181, 1099, 1006, 980, 938, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (dt, J=16.0, 6.8 Hz, 1H), 6.06 (d, J=16.0 Hz, 1H), 3.59 (t, J=6.8 Hz, 2H), 2.24 (s, 3H), 2.21 (q, J=7.2 Hz, 2H), 1.53–1.42 (m, 4H), 1.28 (br s, 10H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 148.9, 131.5, 63.5, 33.0, 32.7, 29.7, 29.6, 29.5, 29.4, 28.3, 27.0, 26.2, 26.0, 18.6, −5.1; MS (EI) m/z (%): 311 (M–CH_3, 4), 269 (M–C_4H_9, 100), 127 (8), 75 (68); HRMS (EI) calcd for $C_{15}H_{29}O_2Si$ $[M-C_4H_9]^+$=269.1937, found 269.1937.

4.8.8. (E)-4-Phenyl-2-butenyl acetate (Table 3, Entry 8). The representative procedure was followed using allylbenzene (30.5 mg, 0.26 mmol), (*Z*)-but-2-ene-1,4-diyl diacetate (91.6 mg, 0.53 mmol) and catalyst **2** (19 mg, 0.005 mmol). Column chromatography on silica gel (eluting with 4% EtOAc/hexanes) afforded the product as a colorless oil (42 mg, 84%). The spectroscopic data obtained for the product were in accord with that previously reported for this compound.[8b]

4.9. General procedure for catalyst recycling

N-Allyl-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (24 mg, 0.10 mmol) and catalyst **2** (7.5 mg, 0.002 mmol) were both added into a Teflon-coated-stir-bar-containing Biotage 2–5 mL microwave reactor vial at rt, and sealed with a septum. H_2O (1.0 mL) was added, via syringe, and the resulting solution was allowed to stir at room temperature for 3 h. Et_2O (3 mL) was then added to the reaction mixture and stirred for 10 s. The reaction mixture was then allowed to separate and the upper (Et_2O) layer was removed by pipette. The aqueous layer was successively washed with Et_2O (3×3 mL). The combined Et_2O extracts layers were evaporated to afforded the crude product, which was examined by 400 MHz

^{1}H NMR spectroscopy to reveal complete conversion of diene and clean formation of the corresponding cyclized product. For the second run, the diene (24 mg, 0.10 mmol) was added again to the same reaction vessel and stirred at rt for another 3 h. The work up was conducted in exactly the same way as described for the first cycle. This reaction was repeated six more times, each using the above diene (24 mg, 0.10 mmol).

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References and notes

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