Modified Routes to the "Designer" Surfactant PQS

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Abstract

PQS
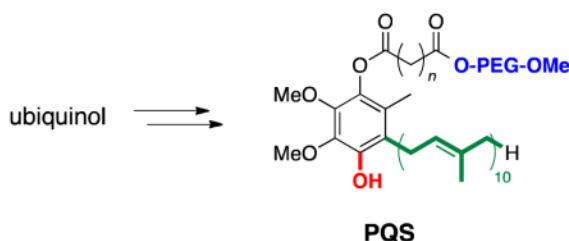
Described herein are newly developed, straightforward entries to "PQS" (**P**olyethyleneglycol
Ubi**Q**uinol **S**uccinate, n = 2), a designer surfactant that serves as precursor to micelle-forming,
covalently bound catalysts for metal-catalyzed transformations in water with in-flask catalyst
recycling.

INTRODUCTION

Catalysis is now considered among the major milestones of last centuries' developments in
organic chemistry. Catalyst recycling, in particular in the case of homogeneous catalysis,
despite its many advantages (*e.g.*, reduced waste and/or more efficient energy usage) still
remains challenging. This is especially true when costly ligands and/or precious metals are
involved. Aqueous biphasic systems have become an important industrial technique and
offer one solution: the catalyst can be recovered from the aqueous phase although the overall
transformation occurs in organic solvent.[1,2] We have previously shown that a variety of
transition metal-catalyzed transformations can be carried out within micellar media,
generated by simply mixing a selected surfactant in water.[3] Organic solvents, therefore, are
no longer needed, as the self-assembled micelles provide the lipophilic interior that serves,
in essence, as the solvent for catalysis; i.e., as nanoreactors *in* water. Moreover, since only
1–2 wt % of surfactant in water easily exceeds the required critical micelle concentration
(CMC), a catalytic amount of the amphiphile is sufficient. While other surfactants typically
contain only lipophilic and hydrophilic subsections, PQS (**P**olyethyleneglycol Ubi**q**uinol
Sebacate) was originally designed to accommodate a third component: an internally
connected catalyst (Figure 1).[4] Hence, the three major subsections of PQS consist of (1) the
readily available hydroquinone, ubiquinol (i.e., the reduced form of CoQ$_{10}$), that supplies
the lipophilicity in its 50-carbon side-chain within which organic substrates are to be
dissolved. Importantly, it also bears a second phenolic handle enabling covalent attachment
of a catalyst that will reside *inside* the nanoreactor of its micellar array; (2)
polyethyleneglycol (PEG-2000), which ensures water solubility; and (3) a linker unit (either

sebacic acid or succinic acid) that connects the lipophilic interior (i.e., ubiquinol) to the hydrophilic exterior (i.e., PEG).

The concept of in-flask catalyst recycling was successfully demonstrated on ring-closing- and cross-metathesis reactions in water employing Grubbs-Hoveyda's first- and second-generation catalysts, which were independently covalently attached to PQS (**4**: PQS-GH-1 and **5**: PQS-GH-2, Figure 2).[4] A study of up to 10 recycles without significant loss of catalyst activity highlighted the potential of the PQS platform. Likewise, a related system based on PQS that does not focus on transition metal catalysts, *e.g.* PQS-proline (**7**) for use in organocatalysis, has recently appeared.[5]

Although a first generation synthesis (i.e., for **1**) gave satisfactory results, limited selectivity in each coupling step using sebacoyl chloride resulted in purification issues.[4] Moreover, scale-up experiments suggested that removal of impurities would be impractical through chromatographic means. Therefore, a synthetically more attractive route to the PQS platform was sought. Herein we describe two novel and improved entries to the designer surfactant PQS-1 (**1**). We also disclose a synthesis of PQS-3 (**3**), a third generation surfactant, employing a succinic acid linker that enhances significantly the availability of the PQS platform.

RESULTS AND DISCUSSION

Initial attempts towards **1** focused on commercially available sebacic acid (**8**), which after anhydride (**9**) formation,[6] was treated with M-PEG-2000 to obtain PEGylated sebacic acid **10**. Subsequent coupling with ubiquinol, either through its acid chloride or via EDCI/DMAP led to PQS-1 (**1**) in high isolated yield and of good purity. To obtain **1** of higher quality, a modified approach from sebacoyl dichloride (**11**) was investigated. Formation of mono-benzylated sebacic acid **12** (57% yield after chromatography) and then coupling and deprotection steps gave mono-PEGylated sebacic acid **10** in high purity following simple precipitation from Et$_2$O. Although the overall yield for PQS-1 (**1**) was generally lower using route **B**, the quality of the material was consistently higher than that obtained via route **A**.[7,8]

The linker unit between ubiquinol and PEG in PQS-1 (**1**) is derived from 10-carbon sebacic acid (**8**), which underwent both mono- and (undesired) diacylation due to the open chain nature of sebacoyl dichloride. Replacement of the C$_{10}$ unit by a C$_4$ fragment originating from succinic acid anhydride would eliminate opportunities for impurities due to reactions at both termini. Thus, starting with (inexpensive) M-PEG-2000 (**14**) and succinic anhydride, mono PEGylated succinic acid **15** was formed in excellent yield (Scheme 2). EDCI-mediated coupling of acid **15** and *N*-hydroxysuccinimide led to activated ester **16**. Neither of these two steps required product purification. Lastly, ester **16** was coupled with ubiquinol[9] in THF to provide PQS-3 (**3**) after straightforward purification on silica gel.[8] This streamlined, cleaner procedure could be successfully repeated on various scales[10] in up to 64% overall yield.

After lyophilization, PQS-3 (**3**) appears as a white, fluffy solid, which readily dissolves in water to provide micelles having an average diameter size of 21 nm, as determined by DLS measurements (Figure 3). By contrast, PQS-1 in water consists of particles of ca. 9 nm. The spherical appearance of these self-aggregated nanoparticles, which can appear, in part, to be agglomerated and, therefore, oblong in shape, was confirmed by cryo-TEM measurements (Figure 4).

To ensure that the minor difference between PQS-1 and PQS-3 (i.e., the 10- vs. 4-carbon linker) does not translate into differences in the observed catalysis, **3** was attached to acid

17[11] to yield carbene precursor **18** (Scheme 3). Subsequent insertion of Ru yielded **6** in good overall yield. PQS-3-GH1 (**6**) appears as a brown solid which is freely soluble in water and forms nano-reactors with an average diameter of 30 nm by DLS (Figure 5).

Cryo-TEM measurements of PQS-3-GH1 (**6**) confirmed the size of these particles and showed their spherical appearance (Figure 6).

Diene **19** was subjected to RCM to yield the cyclized product **20** using **6** as the micelle forming catalyst (Scheme 4). Compared to results obtained previously with **4**,[4a] the newly developed 3rd generation platform (i.e., **6**) functions virtually identically.

New systems, such as PQS-(*R*)-BINAP (**21**) are currently under investigatation for applications to asymmetric Rh- and Pd-catalyzed transformations in water, providing similar options for straightforward catalyst recycling (Figure 7).

CONCLUSIONS

Two alternative synthetic entries to PQS-1 (**1**) are presented. A further improved, third-generation designer surfactant in the PQS series, PQS-3 (**3**), has been developed, the synthesis of which is straightforward, higher yielding than existing routes, and potentially scalable. Both surfactants function equally well when covalently derivatized with ruthenium catalysts, thereby enabling olefin metathesis reactions to be carried out under homogeneous conditions in water at room temperature with in-flask catalyst recycling.

EXPERIMENTAL SECTION

Materials and Methods

Unless otherwise noted, all reactions were performed in oven-dried glassware under an atmosphere of Argon. Poly(ethylene glycol) methyl ether (**13**, M-PEG-2000) was obtained from Aldrich (catalog # 202509). [1]H and ^{13}C spectra were recorded at 22°C on a 400 MHz or 500 MHz NMR spectrometer. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale.

Route A:[7] Synthesis of mono-PEGylated sebacic acid 10

A 250 mL round bottom flask containing a strong magnetic stir bar was charged with poly(ethylene glycol) methyl ether (**14**, 10.00 g, 5.00 mmol, typical M_n 2.000), sebacic acid derivative[6] (1.38 g, 7.50 mmol), 4-dimethylaminopyridine (90 mg, 0.75 mmol) and pyridine (25 mL). After attaching a reflux condenser, the system was purged with argon and heated to 100°C in an oil bath for 4 h whereas all solids dissolved. After cooling the clear solution to room temperature the reaction mixture was acidified with 1.5 N aq. HCl until pH <7 and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and placed overnight under high vacuum to give **10** as a white waxy solid (10.84 g, 4.96 mmol, 99% isolated yield). Alternatively the product can be purified by the following procedure: after concentration and high vacuum (~1 h), the crude product mixture was dissolved in a minimal amount of CH_2Cl_2, a strong stir bar was added and under continuous stirring an excess of Et_2O (~1 L) was added to precipitate out the product (if necessary cooling to −20 °C using an NaCl/ice bath helps the precipitation process). Stirring was continued for 1 h at −20 °C and the formed white precipitate was filtered to yield **10** as a white crystalline solid. Special care needs to be taken during the

filtration step: water has to be excluded and a glass frit should be used. A regular empty glass column (4.5 × 30 cm) with frit was used for this purpose. The cooled suspension was poured into the column and a positive pressure of dried argon was applied immediately. The filtrate was washed twice with cold Et_2O and dried under a stream of argon. To finally dry the product, the stopcock of the column was closed and high vacuum was applied. The product **10** was isolated as a white crystalline solid.

Synthesis of PQS-1 (1)

An oven dried 50 mL round bottom flask (A) containing a magnetic stir bar was charged with MeOPEG sebacic acid **10** (3.08 g, 1.41 mmol), a reflux condenser was attached and the system purged with argon. Thionyl chloride (5 mL) was added through the reflux condenser and heated to reflux for 2 while the evolving gas was bubbled through water and aq. NaOH. The reaction mixture was cooled to room temperature under argon and excess thionyl chloride was taken off using an aspirator. Further drying on high vacuum over night gave a pale orange solid that was dissolved in dry THF (10 mL, distilled from Na/benzophenone) and used in the next step without further purification. In a glove box an oven dried 250 mL round bottom flask (B) was loaded with a strong magnetic stir bar, ubiquinol (4.89 g, 5.65 mmol) and sodium hydride (170 mg, 4.24 mmol, 60% w/w in mineral oil). Outside the glove box, under an atmosphere of argon, dry THF (10 mL, distilled from Na/benzophenone) was added and the suspension was stirred at room temperature for 1 h and cooled to 0 °C. The solution of MeOPEG sebacic chloride **10** in THF (flask A) was added via canulla dropwise to flask B at 0 °C. Flask A was rinsed with additional dry THF (5–10 mL) and transferred to flask B. Under continuous stirring, the orange suspension was slowly warmed to room temperature overnight. The reaction was quenched by the dropwise addition of water and subsequent addition of 1N aq. HCl until pH<7. The mixture was extracted using CH_2Cl_2 (1 × 100 mL, 2 × 50 mL), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield a pale orange oil which can be purified by two different procedures.

Purification A—Short path column. An empty 240g single step column (Thomson Instrument Company) was slurry packed with ~240g of silica gel in Et_2O. The pale orange oil was evenly loaded onto the column using a minimal amount of CH_2Cl_2 and the column was carefully closed using a head space frit. Using a Biotage SP4 system the column was flashed with Et_2O (500 mL, flow rate 45 mL/min), CH_2Cl_2 (500 mL, flow rate 40 mL/min) and eluted with 10% to 15% MeOH/CH_2Cl_2 over 2 L (flow rate 30 mL/min). Fractions containing PEG-ylated material were combined, evaporated and dried on high vacuum over night to yield PQS-1 (**1**) as an amber solid (3.45 g, 1.12 mmol, 86% pure by NMR). Obtained spectral data matched previously reported compound.[4a]

Purification B—Precipitation in ether. The pale orange oil was dissolved in a minimal amount of CH_2Cl_2, a strong stir bar was added and under continuous stirring an excess of Et_2O (~1 L) was added and if necessary cooled to −20 °C using an NaCl/ice bath. Stirring was continued for 1 h to yield a white suspension of PEG-ylated material in Et_2O. Due to the fine particle size all attempts for filtration failed and centrifugation was used instead. Unfortunately the centrifuge used for this purpose could not be cooled during the centrifugation process and led to significant loss of material. Furthermore the centrifuge could only be operated with 6 × 10 mL and was therefore not suited for scale up purposes. An analytical sample (~50 mg) confirmed the purity of PQS.

Route B: Synthesis of mono-benzylated sebacic acid 12

A 100 mL round bottom flask was charged with sebacoyl chloride (10, 8.42 g, 35.2 mmol) and closed with a rubber septum. Et_2O (25 mL) was added and the solution cooled to −78

°C. Benzyl alcohol (2.51 g, 23.2 mmol) and NEt$_3$ (4.9 mL, 35.2 mmol) were added slowly, the cooling bath was removed and the reaction warmed to *rt*. After addition of 1 N HCl, the aqueous phase was extracted with Et$_2$O (3 × 25 mL), the combined organic layers were washed with brine, dried and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with hexanes to 1:1 EtOAc/hexanes gradient to afford mono benzylated sebacic acid **12** (3.90 g, 57%) as a white solid; mp 52–53 °C (recrystalized from hexanes); IR (thin film): 2934, 2914, 2849, 1737, 1699, 1463, 1412, 1299, 1225, 1194, 1172, 940, 906, 745 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ7.39-7.31 (m, 5H), 5.12 (s, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 1.67-1.60 (m, 4H), 1.34-1.27 (m, 8H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 180.0, 173.9, 136.3, 128.7, 128.39, 128.38, 66.3, 34.5, 34.2, 29.22, 29.21, 29.15, 25.1, 24.8; MS (EI) *m/z* (%): 292 (M, 1), 274 (6), 264 (13), 185 (19), 107 (41), 98 (29), 91 (100); HRMS (EI) calcd for C$_{17}$H$_{24}$O$_4$ [M]$^+$ = 292.1675, found 292.1671.

Synthesis of benzyl protected PEG sebacic acid 13

Mono benzylated sebacic acid **12** (2.00 g, 6.85 mmol) was dissolved and refluxed in SOCl$_2$ (4 mL). After 3 h, excess SOCl$_2$ was removed through distillation under reduced pressure. The residue was taken up in dry CH$_2$Cl$_2$ (6 mL). A solution of poly(ethylene glycol) monomethyl ether-2000 (6.17 g, 3.08 mmol) and NEt$_3$ (1.0 mL, 6.85 mmol) in dry CH$_2$Cl$_2$ (6 mL) was added dropwise and stirred over night at *rt*. After addition of 1N HCl, the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 20 mL), and the combined organic layers were dried and concentrated *in vacuo*. The residue was taken up in a minimal amount of CH$_2$Cl$_2$ and an excess of ice cold Et$_2$O was added to form a white precipitate. After further cooling for 1 h, the precipitate was filtered to yield **13** (6.45 g, 92%) as a white solid. IR (neat): 3484, 2885, 2740, 2695, 1734, 1469, 1414, 1360, 1344, 1280, 1235, 1147, 1118, 1062, 947, 844 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36-7.28 (m, 5H), 5.09 (s, 2H), 4.21-4.19 (m, 2H), 3.77-3.46 (m, PEG), 3.36 (s, 3H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.64-1.56 (m, 4H), 1.27 (br s, 8H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 173.9, 173.7, 136.3, 128.7, 128.3, 72.1, 70.75, 70.70, 70.65, 69.3, 66.2, 63.5, 59.2, 34.4, 34.3, 29.2, 25.03, 24.97; MS (ESI): m/2z ~ 1167 (M + 2Na)$^{+2}$.

Synthesis of mono-PEGylated sebacic acid 10

A round bottom flask was charged with **13** (6.41 g, 2.82 mmol) and Pd/C (0.60 g, 0.28 mmol, 5% Pd/C, Fluka) and closed with a rubber septum. MeOH (30 mL) was added and an atmosphere of H$_2$ was provided (balloon). After stirring overnight, the reaction was filtered through Celite, washed with MeOH, and concentrated *in vacuo*. The residue was taken up in a minimal amount of CH$_2$Cl$_2$ and an excess of ice cold Et$_2$O was added to form a white precipitate. After further cooling for 1 h, the precipitate was filtered to afford **10** (6.05 g, 98%) as a white solid. IR (neat): 3527, 2887, 1735, 1639, 1467, 1346, 1281, 1243, 1148, 948, 843 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.24-4.21 (m, 2H), 3.79-3.48 (m, PEG), 3.38 (s, 3H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.64-1.58 (m, 4H), 1.31 (br s, 8H); ^{13}C NMR (125 MHz, CDCl$_3$): δ175.8, 173.5, 71.7-69.0 (m, PEG), 63.1, 58.8, 33.9, 33.7, 28.87, 28.84, 28.79, 24.6; MS (ESI): m/2z ~ 1122 (M + 2Na)$^{+2}$.

Route C: Synthesis of mono-PEGylated succinic acid 15

To a solution of poly(ethylene glycol) monomethyl ether-2000 (**14**, 15.00 g, 7.50 mmol) and succinic anhydride (1.50 g, 15.00 mmol) in toluene (7.5 mL), Et$_3$N (0.53 mL, 3.75 mmol) was added at *rt* with stirring, and the stirring was continued at 60 °C for 8 h. Water was added to the reaction mixture and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with 1N HCl (3 × 50 mL), brine (2 × 30 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo* to afford the poly(ethylene glycol) monomethyl ether-2000 succinate

15 (15.6 g, 99%) as a white solid. IR (thin-film): 3512, 2874, 1734, 1647, 1468, 1349, 1284, 1250, 1109, 949, 844 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.28-4.25 (m, 2H), 3.83-3.46 (m, PEG), 3.38 (s, 3H), 2.69-2.61 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.1, 171.7, 71.4-68.5 (m, PEG), 63.2, 58.5, 28.6, 28.2; MS (ESI): $m/4z \sim 551$ (M + 4Na)$^{+4}$.

Synthesis of activated PEGylated succinic acid 16

Poly(ethylene glycol) monomethyl ether-2000 succinate **15** (2.10 g, 1.00 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to 0 °C. *N*-hydroxysuccinimide (0.14 g, 1.20 mmol), and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDCI, 0.25 g, 1.30 mmol), were then directly added in succession to the mixture as solids. The resulting mixture was stirred at *rt* for 12 h. Water was added to the reaction mixture and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with water, brine, dried, and concentrated *in vacuo* to afford **16** (2.17 g, 99%) as a white waxy solid. IR (thin-film): 2883, 1814, 1784, 1739, 1645, 1468, 1360, 1280, 1234, 1205, 1147, 1116, 1062, 947, 843 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ4.29-4.27 (m, 2H), 3.83-3.46 (m, PEG), 3.38 (s, 3H), 2.97 (t, J = 7.2 Hz, 2H), 2.84 (br s, 4H), 2.79 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.9, 168.9, 167.6, 71.8-68.8 (m, PEG), 64.1, 59.0, 28.6, 26.2, 25.5; MS (ESI): $m/4z \sim 576$ (M + 4Na)$^{+4}$.

Synthesis of PQS-3 (3)

NaH (0.026 g, 0.65 mmol, 60% suspension in mineral oil) was added to a stirred solution of ubiquinol (0.52 g, 0.60 mmol) in THF (5.0 mL) at 0 °C. After addition, the reaction mixture was stirred at 22 °C for 1 h. A solution of **16** (1.10 g, 0.50 mmol) in THF (5.0 mL) was added to the mixture at 0 °C, and the stirring was continued for 30 min. The mixture was then stirred for another 8 h at *rt*. It was then cooled to 0 °C and saturated aqueous NH$_4$Cl was added and then extracted with CH$_2$Cl$_2$. The combined organic layers were washed with water, brine, dried, and concentrated *in vacuo* affording a yellowish liquid, which was purified by flash column chromatography on silica gel eluting with a CH$_2$Cl$_2$ to 1:19 MeOH/CH$_2$Cl$_2$ gradient to afford **3** (0.95 g, 65%, mixture of two regioisomers) as a white waxy solid. IR (thin-film): 3518, 2885, 2740, 1761, 1738, 1663, 1467, 1360, 1343, 1280, 1242, 1147, 1114, 1062, 964, 843 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ5.78 (s, 0.3H), 5.74 (s, 0.7H), 5.12-5.06 (m, 9H), 4.98-4.93 (m, 1H), 4.27-4.24 (m, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 3.70-3.44 (m, PEG), 3.37 (s, 3H), 3.31 (d, J = 6.4 Hz, 1.4H), 3.16 (d, J = 6.4 Hz, 0.6H), 2.94-2.89 (m, 2H), 2.80-2.75 (m, 2H), 2.11-1.96 (m, 39H), 1.74 (s, 2.1H), 1.72 (s, 0.9H), 1.66 (s, 3H), 1.58-1.56 (m, 27H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.04, 171.96, 170.9, 170.7, 145.4, 145.0, 142.1, 141.9, 137.8, 137.6, 135.3, 135.1, 135.0, 134.9, 134.8, 131.1, 128.4, 124.9, 124.4, 124.2, 124.1, 124.0, 121.9, 121.6, 117.9, 71.9-69.0 (m, PEG), 63.9, 60.9, 60.8, 60.6, 60.5, 59.0, 39.7, 29.0, 28.8, 28.7, 26.7, 26.6, 26.0, 25.7, 25.3, 17.7, 16.3, 16.2, 16.0, 12.0, 11.3; MS (ESI): $m/4z \sim 763$ (M + 4Na)$^{+4}$.

Synthesis of carbene precursor 18

3 (0.50 g, 0.17 mmol) was dissolved in CH$_2$Cl$_2$ (2.2 mL) and cooled to 0 °C. 1-(p-Isopropoxy-m-vinylphenyl) propionic acid (**17**)[11] (0.05 g, 0.22 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDCI) (0.04 g, 0.26 mmol), and DMAP (0.008 g, 0.07 mmol) were then directly added in succession to the mixture as solids. Et$_3$N (0.04 mL, 0.30 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$_2$Cl$_2$. 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$_2$O, followed by CH$_2$Cl$_2$ to 1:12 MeOH/CH$_2$Cl$_2$ gradient afforded the compound **18** (0.45 g, 85%, mixture of two regioisomers) as a white foam. IR (thin-film): 2885, 1765, 1737, 1467, 1360, 1344, 1280, 1242, 1147, 1113, 1061, 963, 843

cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ7.39-7.37 (m, 1H), 7.12-7.08 (m, 1H), 7.03 (dd, J = 18.0, 11.2 Hz, 1H), 6.84-6.81 (m, 1H), 5.74 (dt, J = 18.0, 1.6 Hz, 1H), 5.23 (d, J = 11.2 Hz, 1H), 5.13-5.06 (m, 9H), 4.97-4.94 (m, 1H), 4.50 (sep, J = 6.4 Hz, 1H), 4.28-4.25 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.72-3.45 (m, PEG), 3.38 (s, 3H), 3.19-3.14 (m, 2H), 3.06-3.00 (m, 2H), 2.97-2.87 (m, 4H), 2.82-2.76 (m, 2H), 2.10-1.94 (m, 39H), 1.72-1.58 (m, 33H), 1.34 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.0, 170.9, 169.9, 169.7, 169.4, 169.3, 152.9, 142.7, 142.5, 139.9, 139.8, 139.6, 139.5, 134.6, 134.0, 133.8, 131.4, 131.1, 130.1, 127.8, 127.4, 127.0, 125.6, 125.57, 124.0, 123.9, 123.6, 123.5, 123.2, 120.7, 113.8, 113.7, 113.1, 71.2, 70.9-69.3 (m, PEG), 68.2, 63.1, 59.8, 59.6, 58.1, 39.0, 38.9, 34.9, 29.4, 28.2, 28.1, 26.1, 25.9, 25.5, 25.0, 21.5, 17.0, 15.6, 15.4, 11.4, 11.3; MS (ESI): $m/4z$ ~ 839 (M + 4Na)$^{+4}$.

Synthesis of PQS-3-GH1 Catalyst (6)

18 (0.44 g, 0.137 mmol) was weighed into a 25 mL round-bottom flask and dissolved in 6.5 mL of CH$_2$Cl$_2$. (PCy$_3$)$_2$Cl$_2$Ru=CHPh (0.14 g, 0.17 mmol) and CuCl (0.018 g, 0.18 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 dark brown. 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$_2$Cl$_2$ followed by Et$_2$O. Finally, the column was flushed with 8% MeOH/CH$_2$Cl$_2$, at which point the product elutes (brown band). Solvent removal afforded the catalyst **6** (0.49 g, 98%, mixture of two regioisomers) as dark brown foam. IR (thin-film): 2883, 1764, 1737, 1644, 1468, 1449, 1359, 1344, 1280, 1234, 1146, 1113, 1061, 946, 843 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ17.40 (d, J_{PH} = 4.4 Hz, 1H), 7.60-7.58 (m, 1H), 7.56-7.52 (m, 1H), 7.02-7.00 (m, 1H), 5.25 (sep, J = 6.4 Hz, 1H), 5.13-5.10 (m, 9H), 5.00-4.95 (m, 1H), 4.29-4.25 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.70-3.47 (m, PEG), 3.38 (s, 3H), 3.22-3.16 (m, 2H), 2.97-2.87 (m, 4H), 2.82-2.76 (m, 2H), 2.36-2.28 (m, 2H), 2.10-1.98 (m, 39H), 1.81-1.58 (m, 66H), 1.42-1.24 (m, 6H); ^{13}C NMR (200 MHz, CDCl$_3$): δ 279.1, 171.95, 171.86, 170.8, 170.7, 170.3, 170.2, 151.5, 144.0, 143.4, 143.3, 143.2, 140.6, 140.4, 140.3, 135.8, 135.1, 134.8, 134.43, 134.39, 131.1, 129.45, 129.37, 128.4, 128.3, 125.0, 124.9, 124.4, 124.2, 124.0, 123.9, 122.5, 121.1, 116.0, 113.3, 75.5, 71.9, 70.5-69.0 (m, PEG), 63.90, 63.87, 60.6, 59.0, 39.7, 39.6, 35.9, 35.8, 35.7, 35.6, 31.7, 30.1, 29.7, 29.0, 28.8, 28.7, 27.74, 27.7, 26.9, 26.7, 26.67, 26.64, 26.3, 26.24, 26.16, 26.1, 25.7, 22.1, 22.0, 17.7, 16.34, 16.3, 16.0, 12.1; MS (ESI): $m/4z$ ~ 927 (M + 4Na)$^{+4}$.

N-Benzoyl-3-pyrroline (20)

Diene **19** (20 mg, 0.10 mmol) and catalyst **6** (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$_2$O (1.0 mL) was added via syringe, and the resulting solution was allowed to stir at room temperature for 4 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 (40% EtOAc/hexanes) to afford the title compound **20** as a colorless liquid (17 mg, 96%). The ^{1}H NMR spectral data obtained was in accord with data previously reported for this compound.[4a]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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2. For industrial importance of biphasic catalysis, see: Cornils B, Herrmann WA, Eckl RW. Industrial Aspects of Aqueous Catalysis. J Mol Catal A. 1997; 116:27–33.Cornils B. Bulk and Fine Chemicals via Aqueous Biphasic Catalysis. J Mol Catal A. 1999; 143:1–10.Horváth IT, Joo F. Aqueous Organometallic Chemistry and Catalysis. KluwerDordrecht1995Cornils B. Industrial Aqueous Biphasic Catalysis: Status and Directions. Org Proc Res Dev. 1998; 2:121–127.

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4. (a) Lipshutz BH, Ghorai S. Org Lett. 2009; 11:705–708. [PubMed: 19105682] (b) Lipshutz BH, Ghorai S. Tetrahedron. 2010; 66:1057–1063.

5. Lipshutz BH, Ghorai S. Org Lett. 2012; 14:422. [PubMed: 22182221]

6. For a similar procedure, see: Rath P, Gomez-Orellana MI, Vuocolo EA. Aryl Ketone Compounds and Compositions for Delivering Active Agents. U.S. Patent WO/2005/117854. Dec 15.2005

7. For a detailed comparison of the quality of PQS-1 obtained through route **A** or **B**, see SI.

8. PQS is usually obtained as a mixture of regioisomers; PQS-1 (**1** - Route **A**) 2:1; PQS-1 (**1** - Route **B**) 2:1; PQS-3 (**3** - Route **C**) 3:1.

9. Obtained through Zn/HOAc reduction of coenzyme Q_{10}; for procedure, see: Morgan AC, Graves SS, Woodhouse CS, Sikorska M, Walker R, Wilbur DS, Borowy-Borowski H. Water Soluble Ubiquinone Compositions, Prodrugs, and Methods Relating Thereto. PCT. 1996CAN 125:123707.

10. Reactions were performed between 0.25 mmol and 2.2 mmol scales, with consistently good overall yields above 60% in all cases.

11. Garber SB, Kingsbury JS, Gray BL, Hoveyda AH. J Am Chem Soc. 2000; 122:8168–8179.
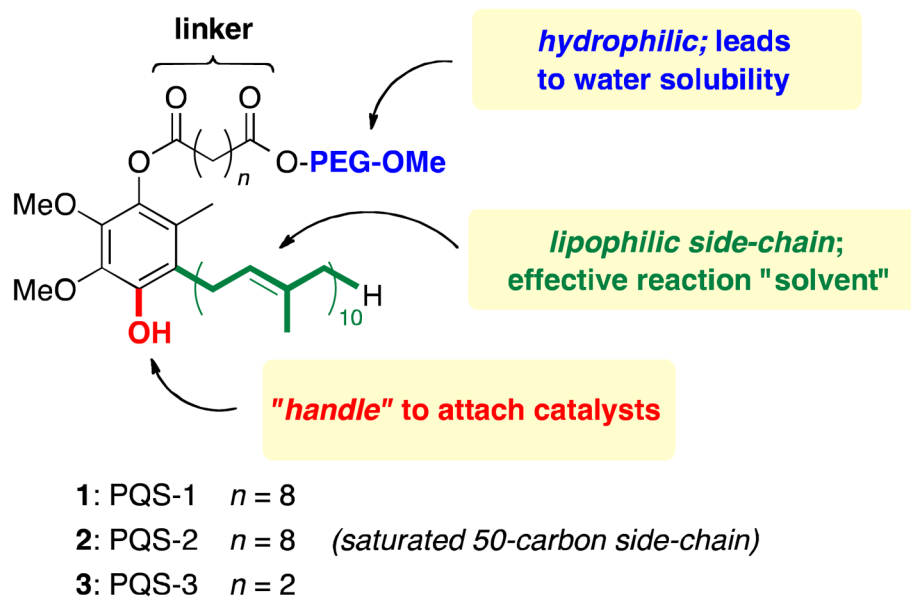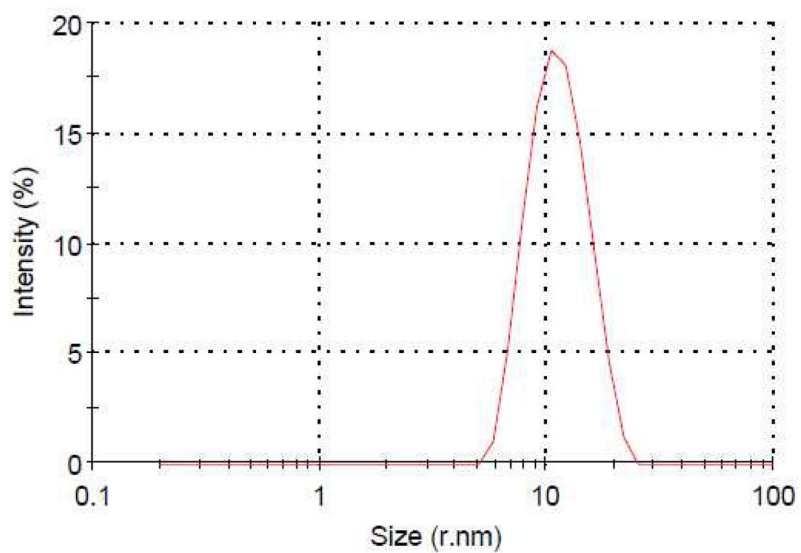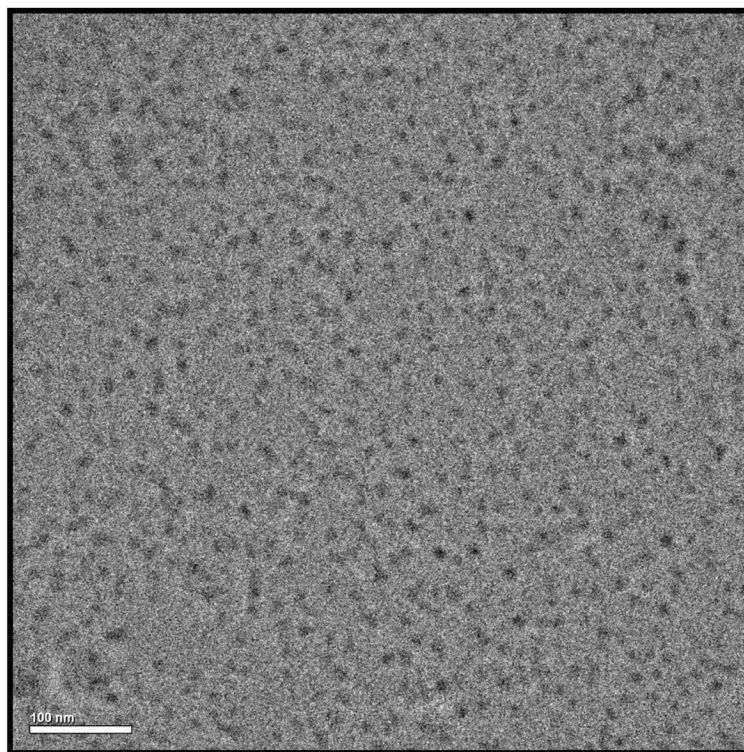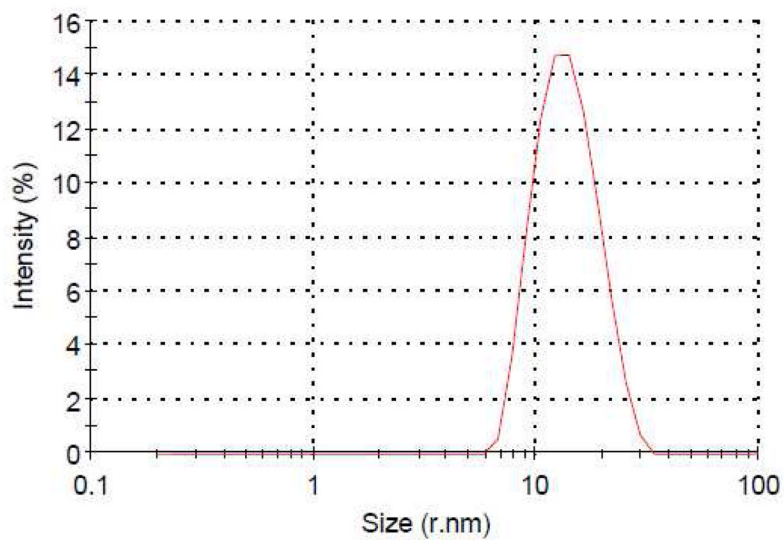
Figure 1.
Designed components of PQS.
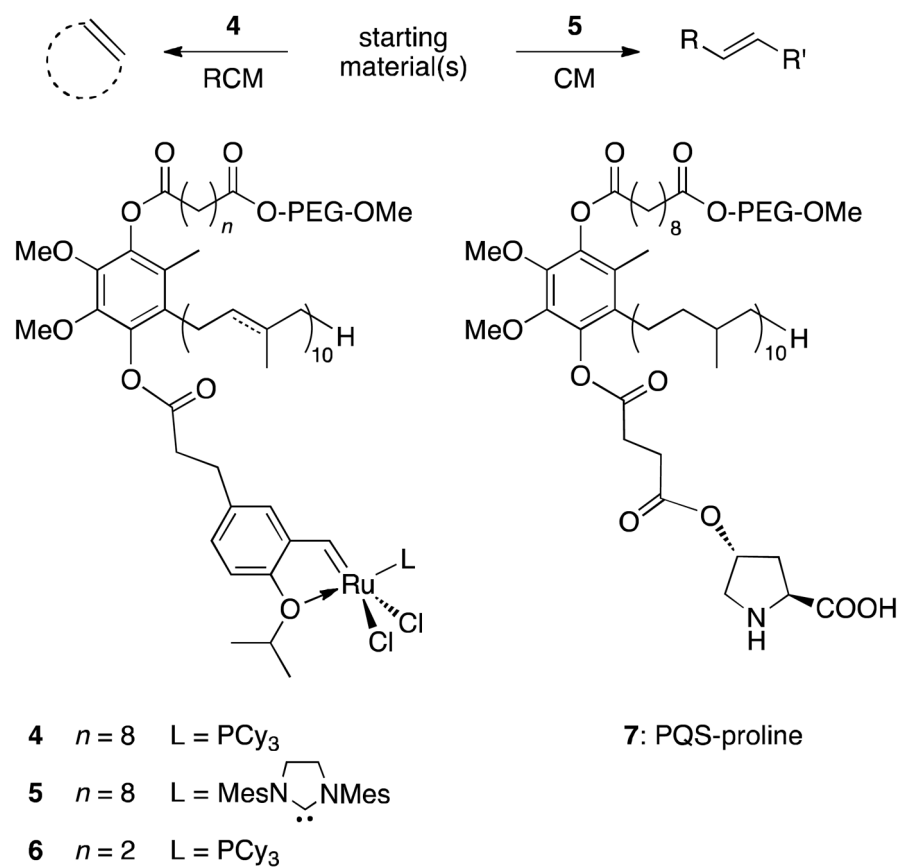
Figure 2.
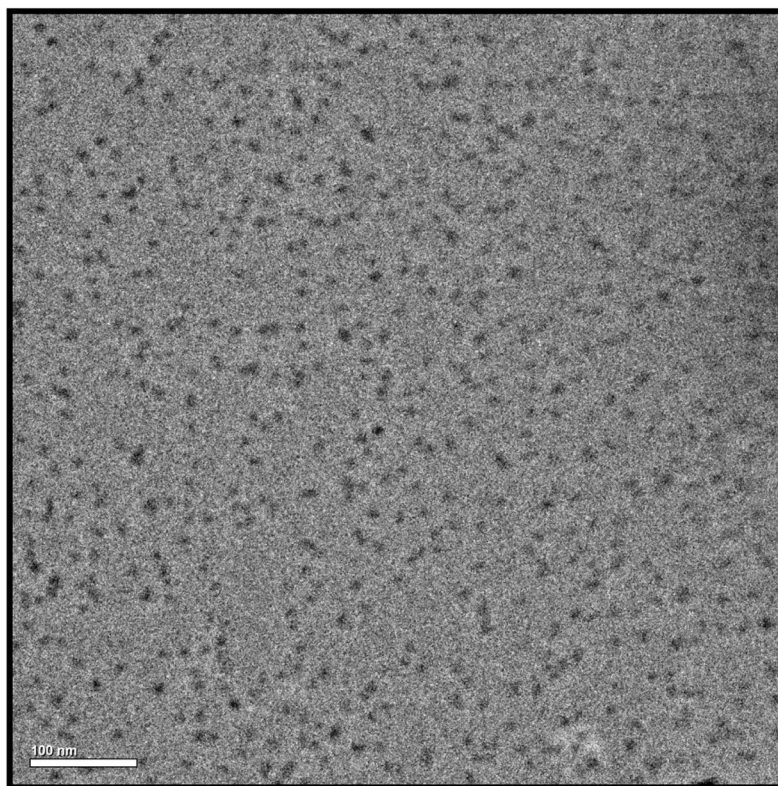PQS as a platform for covalent attachment of a catalyst.

Figure 3.
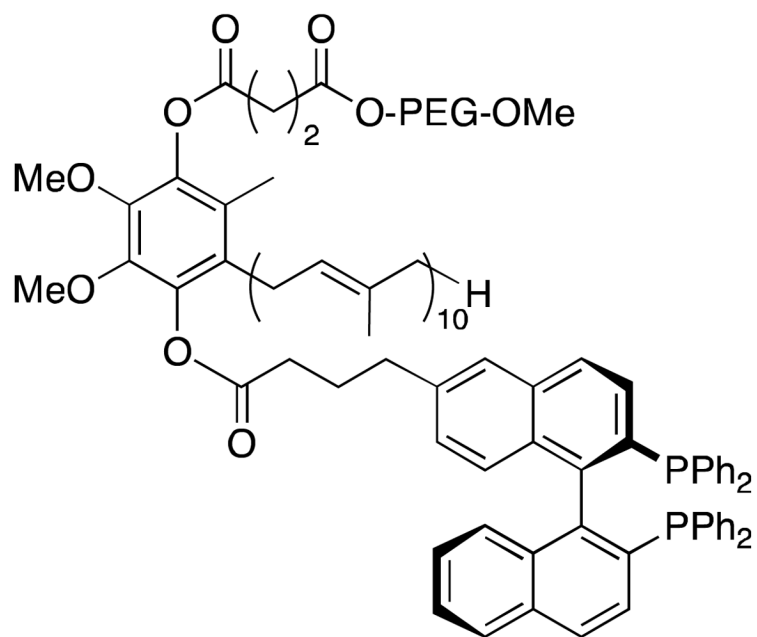Particle size of PQS-3 (**3**) measured by DLS.

Figure 4.
Cryo-TEM measurements of PQS-3 (**3**).

Figure 5.
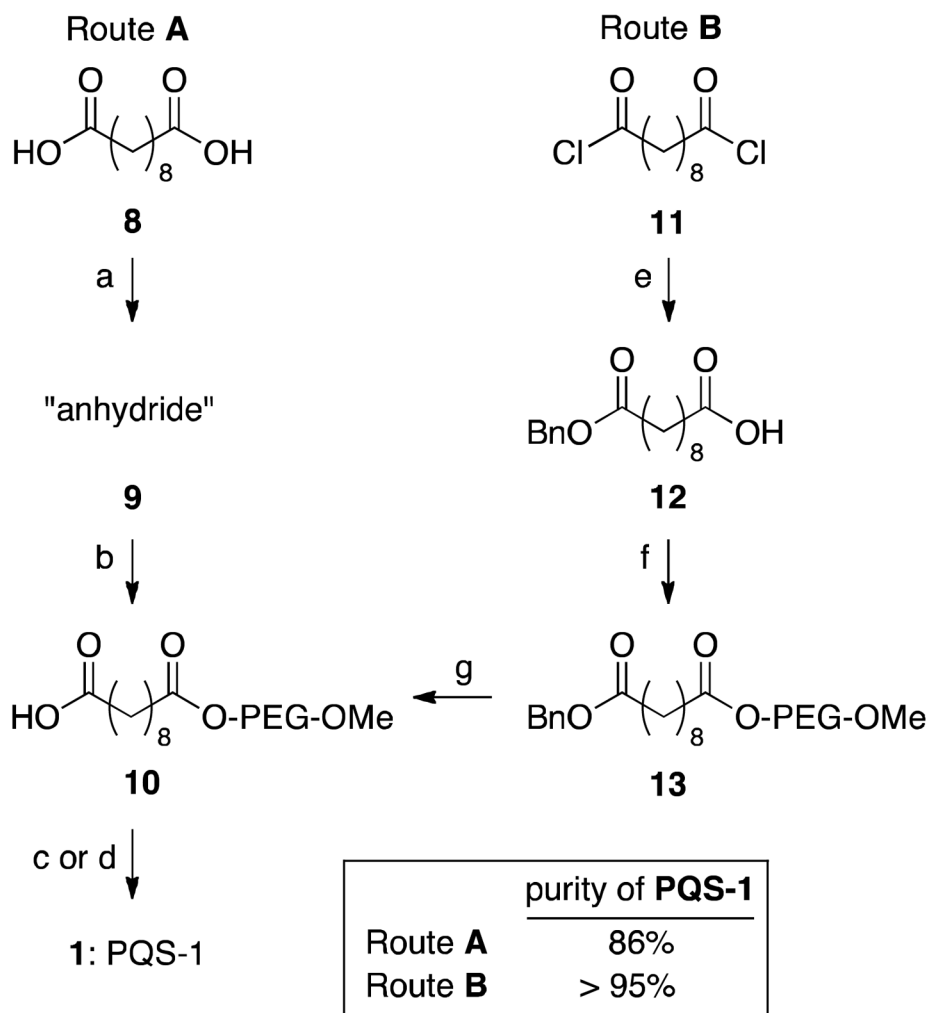Particle size of PQS-3-GH1 (**6**) measured by DLS.

Figure 6.
Cryo-TEM measurements of PQS-3-GH1 (**6**)
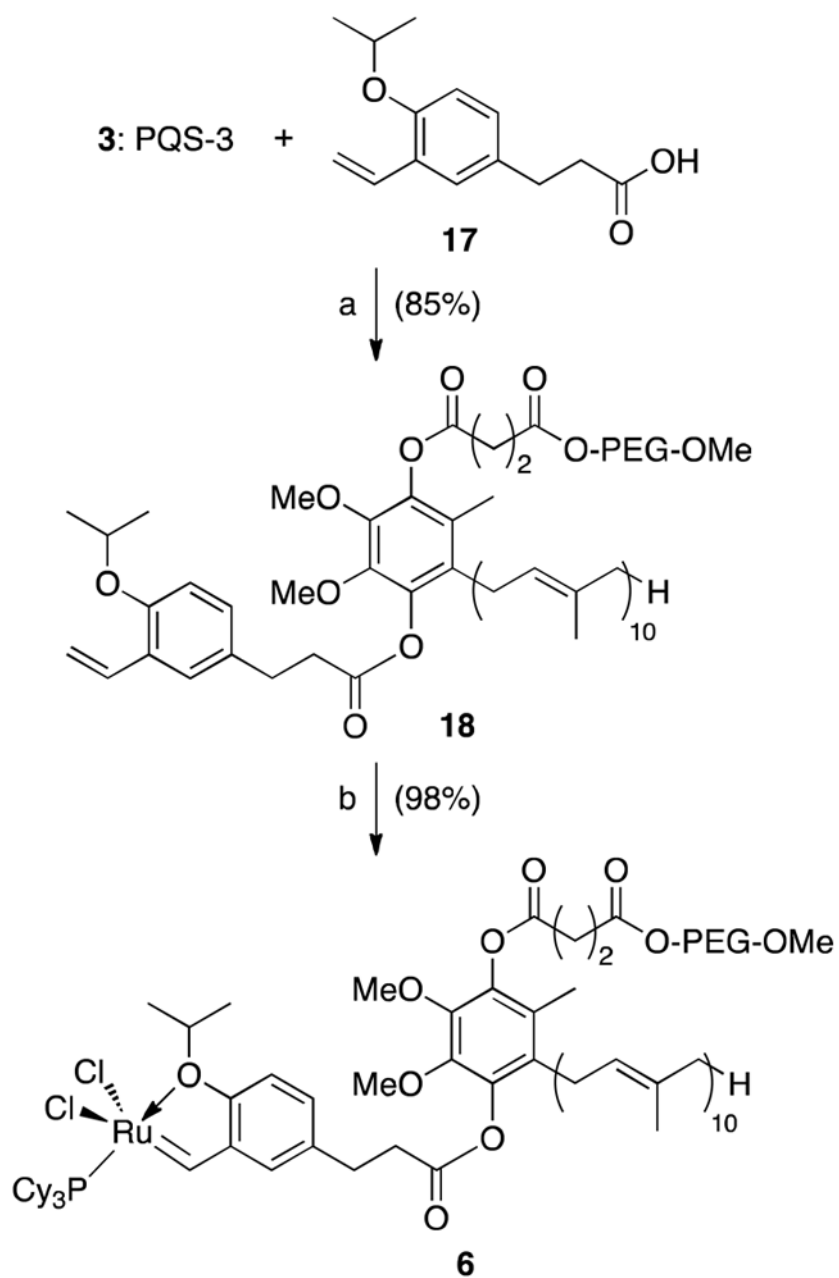
21: PQS-(*R*)-BINAP

Figure 7.
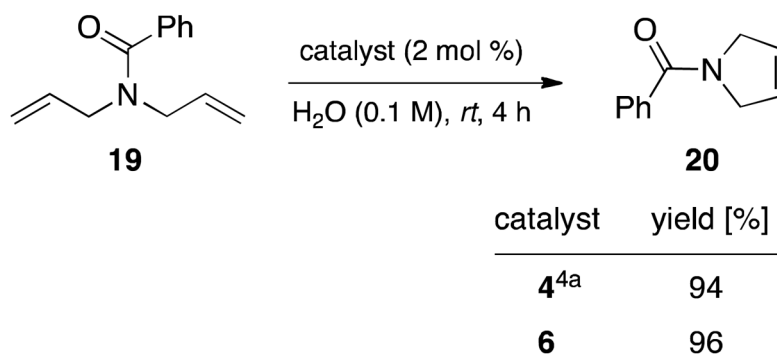PQS-(*R*)-BINAP (**21**) for Rh and/or Pd catalysis.

Scheme 1^a

a Reagents and conditions: (a) Ac$_2$O, reflux, 76%. (b) HO-PEG-Me, DMAP, pyridine, 100 °C, 99%. (c) SOCl$_2$, reflux, then re-dissolved in THF, ubiquinol, NaH, THF, *rt*, 80%. (d) EDCI, DMAP, ubiquinol, NEt$_3$, CH$_2$Cl$_2$, *rt*, 31%. (e) BnOH, NEt$_3$, Et$_2$O, −78 °C to *rt*, then 1 N HCl, 57%. (f) SOCl$_2$, reflux, then HO-PEG-Me, NEt$_3$, CH$_2$Cl$_2$, *rt*, 92%. (g) Pd/C, H$_2$, MeOH, *rt*, 98%.

Route **C**

Scheme 2^a

a Reagents and conditions: (a) succinic anhydride, NEt₃, toluene, 60 °C, 99%. (b) *N*-hydroxysuccinimide, EDCI, CH₂Cl₂, *rt*, 99%. (c) ubiquinol, NaH, THF, 0 °C to *rt*, 65%.

Scheme 3^a

a Reagents and conditions: (a) EDCI, DMAP, NEt$_3$, CH$_2$Cl$_2$, *rt*, 85%. (b) Grubbs 1st generation, CuCl, CH$_2$Cl$_2$, *rt*, 98%.

Scheme 4.

catalyst	yield [%]
4[4a]	94
6	96