Tridentate SCS Palladium(II) Complexes: New, Highly Stable, Recyclable Catalysts for the Heck Reaction

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Abstract: A new pincer-type SCS ligand containing Pd(II) is a simple, robust catalyst for Heck chemistry using a variety of alkene acceptors and aryl iodides. It is less active with aryl bromides. While certain palladium-(II) species insert slowly into the aryl C−H bond of an unsubstituted version of this ligand, the introduction of activating groups into the 5 position of the aromatic ring readily allows quantitative metal insertion. These ligands were synthesized and attached to soluble polymers by simple modification of inexpensive starting materials. For example, both 5-oxy and 5-amido SCS ligands were successfully appended to 5000 M_n poly-(ethylene glycol) via ether or amide linkages, respectively. Both the 5-oxo and 5-amido complexes are active as Heck catalysts in DMF solution in air. The PEG-bound 5-amido-SCS−Pd complex was recycled via solvent precipitation three times with no observed catalyst deactivation. While the 5-amido-SCS−Pd complexes are very robust, their 5-oxo counterparts decompose slowly under certain conditions. These SCS catalysts are analogous to PCP-type catalysts previously reported in the literature but avoid the requirement of an air-sensitive phosphine synthesis.

Introduction

The development of efficient methods to facilitate the recovery and reuse of transition metal complexes remains an important goal in catalytic organic chemistry. Several catalyst recovery techniques have appeared in the literature. Most involve binding the catalyst to an insoluble support (e.g., cross-linked polystyrene) to facilitate catalyst separation after the reaction.[1−3] However, we and others have recently emphasized the utility of soluble polymer supports to achieve this separation.[4−6] Our early work in this area centered on the use of functionalized polyethylene oligomers in catalysis and synthesis.[5−7] More recently, we have employed soluble supports such as poly-(ethylene oxide), poly(*N*-isopropylacrylamide), and polyfluoro-acrylates.[8−13] However, while the element of recyclability alone

greatly extends the overall utility of a precious transition metal catalyst, care must often be taken to avoid a steady deactivation of the catalyst, generally via adventitious oxidation, over several cycles. This problem is especially acute with phosphine-ligated transition metal complexes.[14,15] Therefore, an increasingly important objective within this area is the synthesis of more robust catalysts that can be incorporated into polymer supports.

Palladacycles have been known for over 20 years, but have only recently been investigated as catalysts. Denmark has described chiral bis(oxazoline)palladium(II) catalysts for use in cyclopropanation reactions.[16] Although these catalysts were not very stereoselective, they were very active and the use of the oxazoline ligand avoids the problem of phosphine oxidation. Herrmann and co-workers demonstrated that palladacycles formed from palladium(II) acetate and phosphines such as tris-(*o*-tolyl)phosphine are efficient, thermally stable catalysts for the Heck olefination and Suzuki coupling reactions.[17,18] However, while these phosphine-ligated palladacycles were thermally stable, they were still sensitive to adventitious oxidation. More recently Milstein and co-workers described a phosphorus−carbon−phosphorus (PCP)-type tridentate ligand system useful

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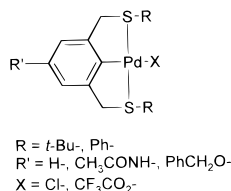
Figure 1. General structure of a tridentate SCS palladium(II) complex. The functionalized complexes are synthesized from isophthalic acid derivatives substituted in the 5 position. For clarity, this position is consistently referred to as the 5 position in all the SCS complexes presented here.

in Heck-type vinylation of aryl halides.[19] These latter PCP–Pd catalysts were both thermally and oxidatively stable.

Motivated by these reports, we reasoned that other general XCX-type ligand systems might lead to new, highly stable catalyst systems. Moreover, with appropriately functionalized ligands, these complexes could be attached to polymer supports to produce robust, easily recyclable catalysts.

Complexes such as those shown in Figure 1 were synthesized and their chemistry explored as early as 1980 by Shaw and co-workers.[20] More recently, similar SCS–Pd complexes have been used by Reinhoudt and co-workers as scaffolds to build self-assembling metallodendrimers.[21] In addition, similar NCN-type complexes have also been described.[22] However, these reports generally do not examine the catalytic potential of these complexes. This paper describes the synthesis of new functionalized SCS–Pd(II) complexes, studies of their stability, and studies of their competence as homogeneous catalysts for Heck chemistry. Preliminary work shows that polymer immobilization of these complexes is also successful; a poly(ethylene glycol)-bound 5-amido SCS–Pd catalyst was readily recyclable.

Results and Discussion

Synthesis, Stability, and Catalytic Properties of Low Molecular Weight SCS Complexes. Our first objective was to explore the catalytic properties of tridentate (SCS) bis-(phenylsulfide)–Pd(II) complexes similar to those reported by Shaw. The necessary SCS ligand **1** was first synthesized from α,α′-dibromo-*m*-xylene via nucleophilic substitution with thiophenol. Our attempts at palladium insertion into the aryl C–H bond of this ligand to prepare an SCS–Pd(II) catalyst were initially frustrated by a very slow insertion reaction. Using Pd(PhCN)$_2$Cl$_2$ in refluxing acetonitrile led mostly to isolation of the bidentate sulfur complex of PdCl$_2$ due to ligand exchange without metal C–H insertion. This problem was solved by pretreatment of the Pd(PhCN)$_2$Cl$_2$ with an excess of AgBF$_4$. Reaction of the more electrophilic Pd(II) species so formed with the SCS ligand under the same conditions resulted in the isolation of an aryl–palladium complexed product as determined by ^{1}H and ^{13}C NMR spectroscopy. Preliminary catalytic studies with the crude **2** formed in this chemistry showed it to be an effective Heck

catalyst. The complex catalyzed the reaction between iodobenzene and methyl acrylate in DMF using Na$_2$CO$_3$ as the base with complete conversion of iodobenzene in 5 h at 105 °C (92% isolated yield). Moreover, no visible decomposition of **2** occurred during this reaction even though it was carried out in the presence of air using undistilled DMF.

Motivated by this result, activating groups were introduced into the 5 position of the aromatic ring in an effort to achieve quantitative yields of analytically pure tridentate, metal-inserted species. The synthesis of a 5-acetamido-SCS ligand **5** and its palladium(II) complex **6** is shown in Figure 3. Esterification of commercially available 5-aminoisophthalic acid, followed by reduction with LAH in THF yielded an amino diol. Subsequent protection of the −NH$_2$ group with acetic anhydride and triethylamine resulted in the acetamido diol. The acetamido dichloride was then formed using equal amounts of SOCl$_2$ and pyridine. Subsequent treatment of this dichloride with thiophenol and K$_2$CO$_3$ in DMF yielded the acetamido-SCS ligand **5**. Treatment of the 5-acetamido-SCS ligand with Pd(PhCN)$_2$Cl$_2$ in refluxing MeCN for 14 h then yielded the complex **6** as a yellow crystalline material. ^{13}C NMR spectroscopic analysis of this material showed clearly that the chemical shift of the 2-position aromatic carbon moved downfield from δ 138.2 to δ 149.8, indicating completion of the metal insertion reaction. Exact mass analysis of **6** showed that the M−Cl peak (484.0027) agreed well with the calculated value (484.0029, 0.41 ppm error).

The thermal, oxidative, acid/base, and water stability of **6** was studied under various conditions. After 20 h at 140 °C in DMF in air, the complex was isolated unchanged. Exposure of **6** to 90% EtOH, 90% EtOH acidified to pH 1 with HCl, and 90% EtOH containing 5 equiv of triethylamine (relative to **6**) at 80 °C for 30 h with exposure to air, also did not affect **6**. Finally, exposure of **6** to a small amount of thiophenol in 90% EtOH at 80 °C for 35 h resulted in no black precipitate of palladium metal.

Catalytic reactions of **6** using various aryl iodides and acceptor alkenes were conducted with DMF or NMP solutions containing 0.1 mol % of **6** at 105−110 °C using either triethylamine or Na$_2$CO$_3$ as the base (eq 1). All of these reactions

base: Et$_3$N or Na$_2$CO$_3$
R: H-, AcNH-, CH$_3$O-, HO$_2$C-
R′: -C$_5$H$_4$N, -Ph, -CO$_2$*t*-Bu, -CO$_2$Me, -CN
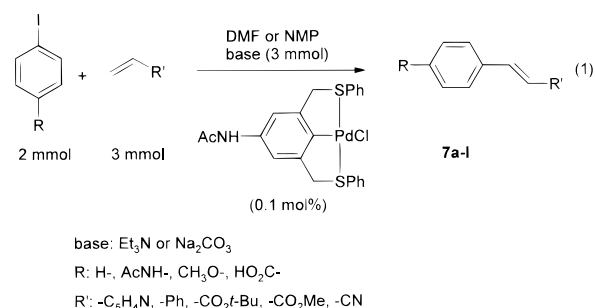
were conducted in air without solvent purification or precautions to avoid oxygen exposure and led to complete conversion of the starting aryl iodide in 5−6 h based on GC analysis. Turnover numbers (TONs) and isolated yields from these reactions are summarized in Table 1.

Since Pd(OAc)$_2$ alone is an active catalyst for Heck reactions when aryl iodides are used, it is important to show that complex **6** is more than just a source of Pd(II). When Heck chemistry was carried out at 80 °C in DMF in air using 0.001 mol % of **6** for the reaction of iodobenzene with methyl acrylate using triethylamine as the base, GC analysis (60 h) showed that this reaction had a turnover number (TON, mol of product/mol of

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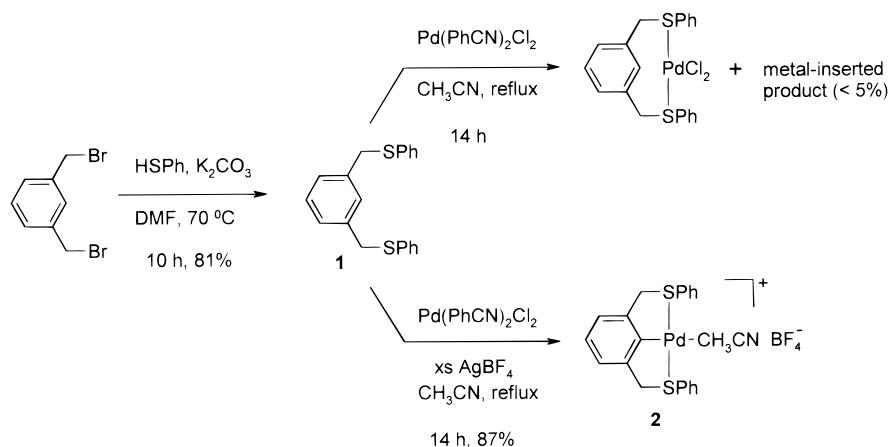
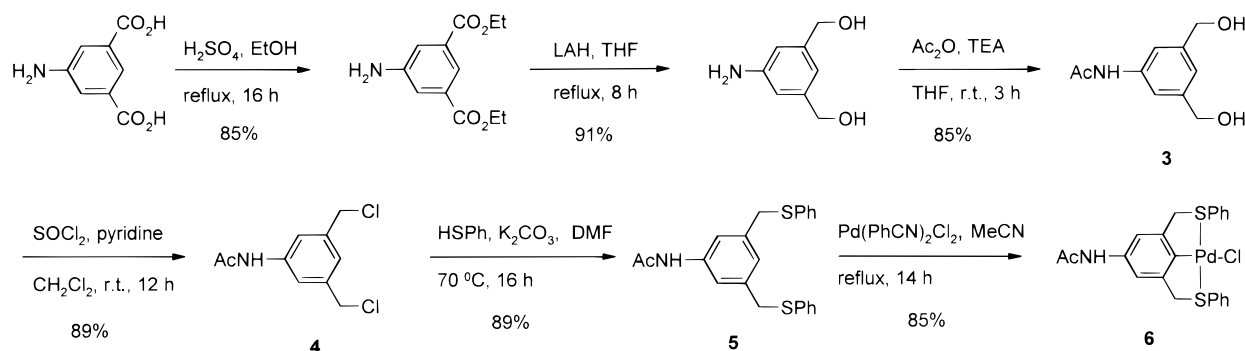**Figure 2.** Synthesis of the unsubstituted SCS−Pd catalyst **2**.

Figure 3. Synthesis of an SCS−Pd complex functionalized para to the C−Pd bond with an acetamido group (**6**).

Table 1. Results from Heck Reactions Using SCS−Pd Catalyst **6**[a]

R	R′	product	yield (%)
−H	−CO₂Me	**7a**	92
−H	−CO₂t-Bu	**7b**	93
−NHAc	−CO₂Me	**7c**	95
−NHAc	−CO₂t-Bu	**7d**	96
−OMe	−CO₂Me	**7e**	94
−COOH	−CO₂Me	**7f**	95
−COOH	−CO₂ t-Bu	**7g**	96
−NHAc	−CN	**7h**	91
−H	−C₅H₄N	**7i**	94
−NHAc	−C₅H₄N	**7j**	96
−H	−Ph	**7k**	92
−OMe	−Ph	**7l**	93

[a] All reactions were carried out in air at 110 °C for 5−6 h using 0.1 mol % of catalyst **6**. For all reactions, the turnover number (TON) is 1000 and the yield listed is for pure isolated product (based on ^{1}H and ^{13}C NMR spectroscopy). GC yields for all the products were quantitative.

catalyst) of 70000. Under the same conditions, 0.007 mol % of Pd(OAc)₂ had a TON of 1400. A black solid, presumably Pd(0), also precipitated from the reaction solution when using Pd(OAc)₂ under these conditions.

However, while **6** was an effective catalyst for Heck chemistry using aryl iodides, it was ineffective with aryl bromides. After 10 h, no reaction was observed between 3,5-dimethylbromobenzene and *tert*-butyl acrylate using 5 mol % of **6** at 140 °C. Also, 4-bromoacetanilide failed to react with either methyl acrylate or 4-vinylpyridine in the presence of 0.1 mol % of **6** within 14 h at 135 °C. After 20 h at 140 °C, GC analysis showed only 30% conversion using 2 mol % of **6** and *p*-bromoanisole and *tert*-butyl acrylate as substrates.

In an effort to build a more electron-rich palladium center that would be more reactive toward aryl bromides, the 5-benzyloxy-SCS−Pd complex **9** was synthesized. The free 5-ben-

zyloxy ligand **8** was prepared in a manner analogous to that described for the 5-acetamido-SCS ligand, starting with the commercially available 5-hydroxyisophthalic acid (Figure 4).

Milder palladation conditions were sufficient for the synthesis of **9**; the insertion reaction was complete in 2.5 h using palladium(II) trifluoroacetate at room temperature. When more vigorous conditions were used (e.g., Pd(PhCN)₂Cl₂ in refluxing acetonitrile), large amounts of black precipitate formed during the reaction; the isolated product was a mixture of metal inserted and noninserted products. The evident decomposition observed under these conditions raised questions regarding the stability of this complex to potential reaction conditions. Indeed, when stability experiments analogous to those for **6** were performed on pure **9**, slow degradation of the complex did occur in acetonitrile under both acidic and basic conditions. ^{1}H NMR spectra of the complex during these experiments showed the steady disappearance of the singlet at δ 6.74 (2H, protons meta to the C−Pd bond) and the appearance of signals at δ 6.91 and 6.79 in a 1:2 integrated ratio, indicating cleavage of the C−Pd bond. In view of these results, catalytic experiments were not performed using **9**.

Synthesis and Catalytic Properties of Poly(ethylene glycol)-Bound SCS−Pd Complexes. Efforts to bind SCS−Pd complexes to a soluble polymer support were carried out concurrently with work on synthesizing low molecular weight complexes. Thus, the first PEG-bound complex synthesized was **14**, in which the SCS ligand is connected to the polymer via an ether linkage. The synthetic scheme depicted in Figure 5 was initially chosen as the most direct route to a poly(ethylene glycol)-bound SCS catalyst. The synthesis paralleled that outlined for the low molecular weight 5-amido counterpart **6**. Purification at each step of the process was achieved by recrystallization of the polymer from 2-propanol. The soluble
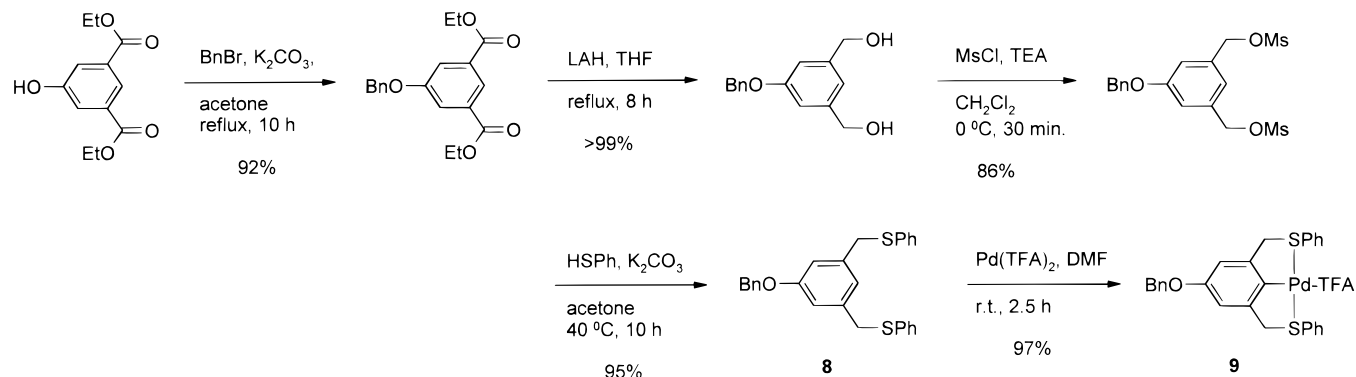
Figure 4. Synthesis of an SCS−Pd complex functionalized para to the C−Pd bond with a benzyloxy group (**9**).
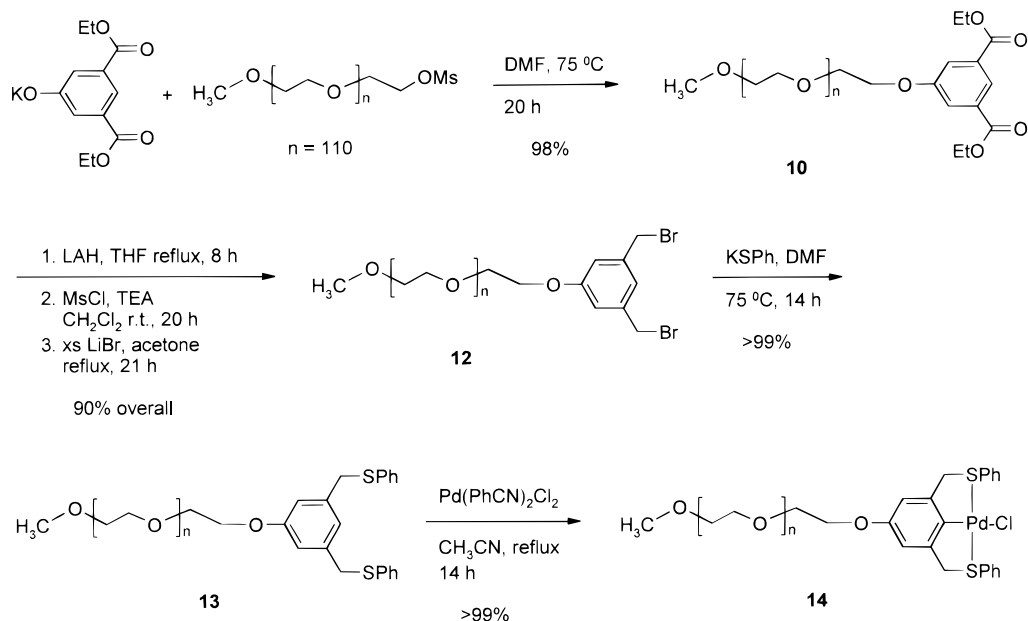

Figure 5. Synthesis of the poly(ethylene glycol)-supported 5-oxo-SCS−Pd catalyst **14**.

intermediate products were readily characterized by ^{1}H NMR spectroscopy.

The first step in this synthesis involved the coupling of the ligand scaffold to a PEG support. Diethyl 5-hydroxy isophthalate was treated with potassium *tert*-butoxide and the phenolate so formed was allowed to react with mesylate-terminated 5000 molecular weight (M_n) poly(ethylene glycol) monomethyl ether. The product of this reaction, a PEG-bound isophthalate diester, was then subjected to the same synthetic protocol (reduction, conversion to good leaving groups, and substitution with thiophenol) as that previously described. The ligand **13** was then treated with the palladium precatalyst Pd(PhCN)$_2$Cl$_2$ to give the final product **14**. ^{1}H NMR spectroscopy clearly showed the disappearance of the signal from the C-2 proton of the central aromatic ring (present at 6.82 δ in **13**) and the shifting of the singlet for the C-4 and C-6 protons from δ 6.71 in **13** to δ 6.59 in the metal-inserted product **14**.

In catalytic experiments, **14** was an active Heck catalyst under conditions similar to those used for **6**. Several reactions were run in DMF in air at 110 °C; completion times for the reactions were similar to those for **6** (5−6 h). Isolated yields for these reactions are summarized in Table 2. However, catalyst **14** did slowly decompose like its low molecular weight analogue. A black precipitate of palladium metal and reformation of the original bis(phenyl sulfide) group based on ^{1}H NMR spectroscopic analysis indicated that **14** would not be recyclable.

Table 2. Results from Heck Reactions Run with PEG-Bound Catalyst **14**[a]

R	R′	product	yield (%)
−NHAc	−CO$_2$Me	**7c**	95
−NHAc	−CO$_2$t-Bu	**7d**	71
−NHAc	−C$_5$H$_4$N	**7j**	93
−H	−CO$_2$Me	**7a**	83
−H	−CO$_2$t-Bu	**7b**	>99
−H	−C$_5$H$_4$N	**7i**	74

[a] All reactions were carried out in air at 110 °C for 5−6 h using 0.1 mol % of catalyst **14**. For all reactions, the turnover number (TON) is 1000 and the yield listed is for pure isolated product (based on ^{1}H and ^{13}C NMR spectroscopy). GC yields for all the products were quantitative.

The synthesis of a more stable 5-amido SCS complex is shown in Figure 6. The 5-acetamido-SCS ligand **5** was hydrolyzed using NaOH in ethanol, yielding a 5-amino-SCS species. Treatment of this amino SCS ligand with glutaric anhydride yielded an acid-terminated SCS ligand. This ligand was then converted to the Pd complex **17** by treatment with Pd(PhCN)$_2$Cl$_2$. In addition to ^{1}H NMR, ^{13}C NMR, and HRMS analyses, **17** was also characterized by X-ray crystallography. The crystal structure of **17** is shown in Figure 7.

The structure of **17** shows that the *S*-phenyl groups provide a C_2-chiral ligand environment for the Pd center. ^{1}H NMR spectroscopy indicates that rapid interconversion of the two chiral sulfur centers of **17** occurs. The signal for the four benzyl
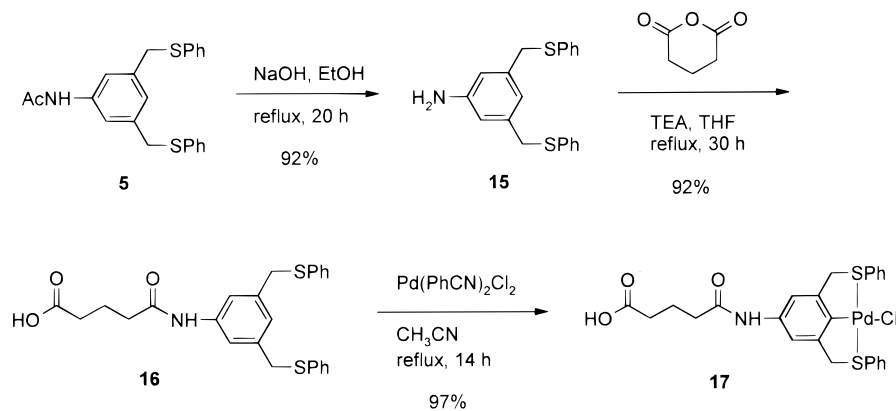
Figure 6. Conversion of the 5-acetamido-SCS ligand **5** to an acid-terminated species **17**.
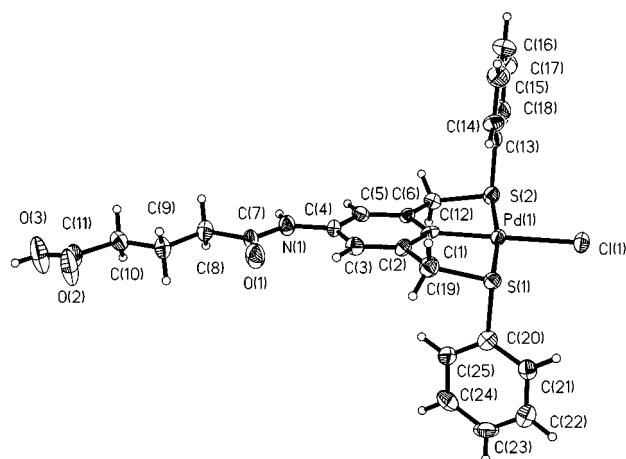

Figure 7. X-ray crystal structure of the acid-terminated SCS−Pd complex **17**; thermal ellipsoids are 50% probability. Selected bond distances: C_1−Pd_1 (1.97 Å), Pd_1−S_1 (2.30 Å), Pd_1−S_2 (2.30 Å), Pd_1−Cl_1 (2.41 Å). Additional crystallographic information is given in Table 3 in the Experimental Section.

protons of **17** was a broad singlet at room temperature, but this singlet sharpened significantly at higher temperatures. This structure and dynamic behavior suggest that other *S*-chiral ligands such as **17** can be prepared. We are currently working toward that goal.

To append the acid-terminated species **17** to a PEG support via an amide linkage, the hydroxyl end group of the polymer was first converted to an amine using a previously reported procedure.[23] As shown in Figure 8, the monomethoxy PEG was converted to the mesylate and then reacted with potassium phthalimide in DMF. The resulting PEG-phthalimide was cleaved with hydrazine in ethanol to yield an amine-terminated PEG. The coupling step was accomplished simply by activating **17** with dicyclohexylcarbodiimide (DCC) and then allowing it to react with the PEG-amine. ^{1}H NMR spectroscopic analysis of the resulting PEG-bound 5-amido-SCS−Pd complex **18** showed complete conversion of the amine group.

The PEG-bound catalyst **18** was readily recycled after a typical reaction. The reactions shown in Figure 9 were run under conditions similar to those previously described: 115 °C in DMF in air, using TEA and 0.1 mol % **18**. GC analysis showed that both reactions were complete in under 7 h. Upon the completion of each cycle, the reaction solution was poured into diethyl ether, precipitating the catalyst, which was isolated and redissolved in DMF for use in the next cycle. After a simple extractive

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workup, the pure (by ^{1}H and ^{13}C NMR spectroscopy) Heck coupling products were isolated. Three cycles were run for each reaction; the resulting isolated yields are summarized in Figure 9. No loss or deactivation of the catalyst is observed in this recycling protocol. GC analysis of each cycle yielded a constant rate of conversion over all three cycles for both reactions. This suggests that the actual turnover number for catalyst **18** was much higher than that represented by a single cycle. Whereas a conventional catalyst turnover number represents a single reaction, the effective TON for **18** was limited only by the number of cycles run.

Conclusions

New tridentate SCS-type palladium(II) complexes are effective catalysts for the Heck reaction between aryl iodides and alkene acceptors. These catalysts were synthesized from readily available starting materials using straightforward chemistry. Changing the group occupying the 5 position of the central aromatic ring influenced the stability of the complex. While both the 5-oxy- and 5-amido-SCS catalysts performed well under homogeneous conditions in DMF, only the 5-amido complexes such as **6** had long-term stability to the reaction conditions. Thus, complex **17** was then synthesized and subsequently coupled to an amine-terminated PEG support, yielding a highly stable, recyclable catalyst. These new SCS catalysts are attractive due to their simple, efficient synthesis and modification as well as their high durability and easy recyclability.

Experimental Section

General. THF was distilled from sodium-benzophenone ketyl, CH_2Cl_2 was distilled from calcium hydride, and DMF was distilled from and stored over molecular sieves. All other reagents and solvents were obtained from commercial sources and were generally used without further purification. Gas chromatographic analyses were performed on a Shimadzu instrument equipped with a 15-m SPB-5 (poly(5%-diphenyl-95%-dimethylsiloxane)) normal phase fused silica capillary column (0.53 ID). ^{1}H NMR spectra were recorded on Varian VXR-300 or Unity p300 spectrometers at 300 MHz. Chemical shifts are reported in ppm using either tetramethylsilane (TMS, 0.00 ppm) or hexamethyldisilane (HMDS, 0.055 ppm) as internal standards. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ or DMSO-d_6 as the internal reference. Crystallographic data for **17** were collected on a Siemens P4 instrument using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The data were corrected for Lorentz and polarization effects and absorption using semiempirical corrections from ψ-scans. Minimum and maximum absorption corrections for **17** were 0.835 and 0.932, respectively. The structure of **17** was solved and refined using the SHELX-97 package.[24] Refinement was by full-matrix least-squares on F^2 using all data. The weighting scheme was w =
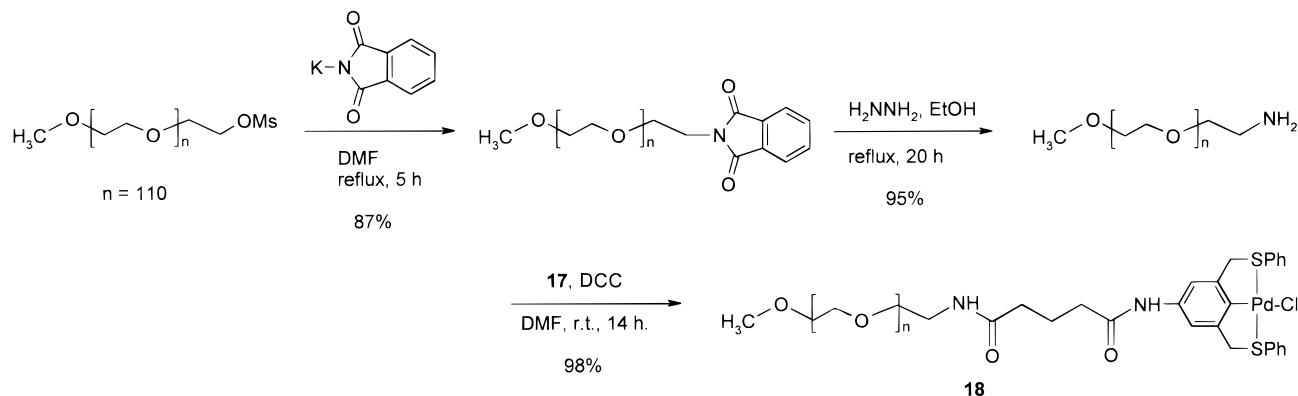
Figure 8. Attachment of complex **17** to a poly(ethylene glycol) support.
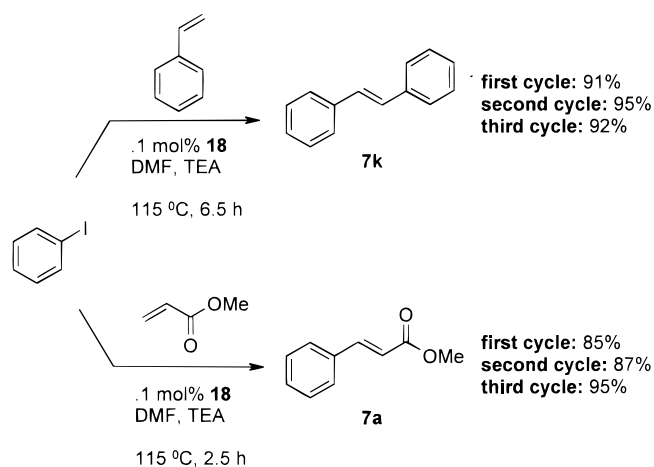

Figure 9. Recycling of the PEG-bound 5-amido-SCS−Pd catalyst **18**. The catalyst was recycled after each reaction by solvent precipitation (diethyl ether).

$1/[\sigma^2(F_o^2) + 28.58P]$ where $P = (F_o^2 + 2F_c^2)/3$. Hydrogen atoms were included in the calculated positions and treated as riding atoms. The ORTEP plot in Figure 7 was generated using ORTEP3 for Windows.[25] For simplicity associated solvent molecules ($^3/_2$CH$_3$CN) were removed from the plot. Accurate mass measurements of compounds **6**, **8**, and **17** were made using a VG Analytical 70S high resolution, double focusing, magnetic sector (EB) mass spectrometer in the +FAB ionization mode; all determinations resulted in <1 ppm error from the theoretical accurate mass values.

Synthesis of N-Acetyl-3,5-bis(hydroxymethyl)aniline (3). 3,5-Bis-(hydroxymethyl)aniline was synthesized in two steps from 5-aminoisophthalic acid according to previously reported procedures.[26,27] Triethylamine (2.02 mL, 14.5 mmol) and acetic anhydride (1.37 mL, 14.6 mmol) were then added to a solution of this material (2.40 g, 14.5 mmol) in 40 mL of THF. The reaction solution was allowed to stir at room temperature; within 10 min, large amounts of a white precipitate, the product acetamido diol, had formed. The reaction was allowed to stir for an additional 3 h. The product was isolated by filtration, washed with portions of THF, and dried under vacuum, yielding 2.56 g (85%) of a white solid: ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3H), 4.41 (s, 4H), 5.18 (br s, 2H), 6.90 (s, 1H), 7.40 (s, 2H), 9.92 (s, 1H).

Synthesis of N-Acetyl-3,5-bis(chloromethyl)aniline (4). A suspension of **3** (2.00 g, 9.66 mmol) in 50 mL of methylene chloride was prepared. Pyridine (1.72 mL, 21.3 mmol) was added and the resulting mixture was cooled to 0 °C. Then, thionyl chloride (1.55 mL, 21.3

mmol) was added dropwise to the mixture, resulting in the eventual dissolution of the starting material. The ensuing homogeneous solution was stirred at room temperature for 18 h. After the reaction, the organic phase was washed with water (3 × 30 mL), 1 N HCl (2 × 10 mL), and brine (2 × 10 mL) and then dried over MgSO$_4$. The solvent was removed under reduced pressure and the isolated yellowish solid was dried under vacuum, yielding 2.10 g (89%) of the 5-acetamido dichloride: ^{1}H NMR (CDCl$_3$) δ 2.10 (s, 3H), 4.51 (s, 4H), 7.12 (s, 1H), 7.57 (s, 2H).

Synthesis of N-Acetyl-3,5-bis(phenylthiomethyl)aniline (5). A solution of **4** (2.10 g, 8.60 mmol) in 30 mL of DMF was prepared. To this solution was added potassium carbonate (2.97 g, 21.5 mmol) and thiophenol (1.78 mL, 17.3 mmol). The reaction mixture was heated at 70 °C for 16 h. After this time, it was then poured into 400 mL of H$_2$O and chilled at 5 °C for 24 h to induce precipitation of the product as an off-white solid material. The product was collected by filtration and washed with saturated Na$_2$CO$_3$ (2 × 20 mL), 1 N HCl (1 × 10 mL), and water (2 × 20 mL). The solid was then dried under vacuum, yielding 2.99 g (89%) of the product 5-acetamido SCS ligand: ^{1}H NMR (CDCl$_3$) δ 2.15 (s, 3H), 4.01 (s, 4H), 6.95 (s, 1H), 7.10−7.32 (m, 8H), 7.34 (s, 2H), 7.43 (m, 2H).

Palladation of N-Acetyl-3,5-bis(phenylthiomethyl)aniline (6). The ligand **5** (2.0 mmol, 0.70 g) was dissolved in 10 mL of MeCN under N$_2$ in a flame-dried flask. Then Pd(PhCN)$_2$Cl$_2$ (2.0 mmol, 760 mg) was added and the mixture was first stirred for 1 h at room temperature and then refluxed for 14 h. The hot solution was filtered rapidly to remove any insoluble material. The filtrate was allowed to cool to 25 °C and the precipitated yellow crystals were collected, washed with hexane (2 × 5 mL), and dried under vacuum to yield 0.88 g (85%) of the pure product **6**: ^{1}H NMR (DMSO-d_6) δ 2.04 (s, 3H), 4.83 (s, 4H), 7.30 (s, 2H), 7.49−7.53 (m, 6H), 7.87−7.90 (m, 4H), 9.86 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.88, 49.91, 113.08, 129.40, 129.53, 130.66, 132.22, 132.76, 136.36, 149.78 (C−Pd), 168.06; HRMS m/z 484.0027 (calcd for C$_{22}$H$_{20}$NOS$_2$Pd (M−Cl) 484.0029, (0.41 ppm error)).

General Procedure for Using 6 in Homogeneous Heck Reactions (7a−l). A 20-mL vial was charged with 2 mmol of aryl iodide, 3 mmol of olefin, 3 mmol of triethylamine or Na$_2$CO$_3$, 0.002 mmol of the SCS−Pd catalyst (**6**), and 10 mL of DMF or NMP. The mixture was stirred at 105−110 °C in air and the reaction progress was analyzed by GC. The conversion was generally greater than 98% after 5 h and the average isolated yield was 93%. The product was isolated by pouring the reaction mixture into excess water and either collecting the precipitate or washing the aqueous phase several times with diethyl ether. The structures of the isolated products were confirmed by ^{1}H and ^{13}C NMR analysis. All of the products are known compounds.[28]

Synthesis of O-Benzyl-3,5-bis(phenylthiomethyl)phenol (8). O-Benzyl-3,5-bis(phenylthiomethyl)phenol was prepared in five steps from 5-hydroxyisophthalic acid in a manner analogous to that previously reported:[21] ^{1}H NMR (CDCl$_3$) δ 3.97 (s, 4H), 4.83 (s, 2H), 6.75 (s, 2H), 6.81 (s, 1H), 7.17−7.42 (m, 15H); ^{13}C NMR (CDCl$_3$) δ 38.77, 69.78, 113.99, 121.84, 126.24, 127.40, 127.85, 128.43, 128.74, 129.72, 136.11,

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136.67, 139.04, 158.80; HRMS *m/z* 428.1268 (calcd for $C_{27}H_{24}OS_2$ 428.1264 (0.93 ppm error)).

Palladation of *O*-Benzyl-3,5-bis(phenylthiomethyl)phenol (9). A solution of **8** (0.502 g, 1.17 mmol) in 3 mL of dry, freshly distilled DMF was added to a flame-dried flask and the system sealed. The oxygen in the flask was removed with a vacuum pump and replaced with dry N_2; the flask was allowed to purge with nitrogen for 15 min. Three pump/purge cycles were performed. Then, palladium(II) trifluoroacetate (388 mg, 1.17 mmol) dissolved in 1 mL of DMF was added via syringe. The resulting solution took on the deep purple color of the dissolved Pd(TFA)$_2$. The reaction was stirred at room temperature and its progress monitored by TLC (heptane). The reaction was complete after 2.5 h, after which the reaction solution was poured into 10 mL of diethyl ether, precipitating the product as a sticky purple material. This mixture was cooled at −5 °C for 16 h to solidify the product. The supernatant was poured off and the product washed with further portions of ether (to remove traces of byproduct TFA) and then dried under vacuum to yield 0.647 g (97%) of the product **9**: ¹H NMR (CDCl₃) δ 4.71 (br s, 4H), 4.99 (s, 2H), 6.73 (s, 2H), 7.30−7.41 (m, 5H), 7.22 (m, 6H), 7.82 (m, 4H); ¹³C NMR (CDCl₃) δ 50.62, 70.14, 109.60, 127.39, 128.09, 128.61, 129.66, 130.18, 131.63, 132.90, 136.53, 149.47 (C−Pd), 156.98. Due to the observed instability of **9**, spectral data were obtained as quickly as possible after isolation. Even NMR samples of **9** gradually formed a black precipitate (presumably Pd metal) on standing. Additionally, HRMS analysis was not performed on **9**; the immediate precursor, ligand **8**, was, however, characterized by this method.

Synthesis of MeO-PEG$_{5000}$-Isophthalic Acid Diethyl Ester (10). To a solution of diethyl 5-hydroxy isophthalate (1.43 g, 6.00 mmol) in freshly distilled THF was added potassium *tert*-butoxide (0.674 g, 6.00 mmol). Upon addition of the base, the solution turned a bright yellow-orange color. The solution was stirred at room temperature for 30 min. The THF was removed under reduced pressure and the salt residue was dissolved in 10 mL of DMF. This solution was added to a solution of PEG-mesylate (10.0 g, 2.0 mmol; synthesized using a procedure analogous to that previously reported[23]) in 50 mL of DMF. The resulting homogeneous solution was stirred at 75 °C for 20 h. After the reaction, the solution was filtered through Celite to remove insoluble materials and the filtrate was acidified to pH 4 with concentrated HCl. The solvent was then removed from the filtrate under reduced pressure. The residue was redissolved in 75 mL of MeOH. This solution was poured into 300 mL of diethyl ether, with stirring, to precipitate the product as a white solid. This solid was isolated, recrystallized from 2-propanol, and washed with further portions of cold 2-propanol before being dried under vacuum to yield 9.8 g (98%) of the product **10**: ¹H NMR (CDCl₃) δ 1.40 (t, 6H), 3.28−3.85 (PEG, 440H), 4.21 (t, 2H), 4.39 (q, 4H), 7.75 (s, 2H), 8.25 (s, 1H).

Synthesis of MeO-PEG$_{5000}$-Diol (11). A solution of **10** (9.62 g, 3.84 mmol) in dry, freshly distilled THF (150 mL) was prepared. To this solution was added lithium aluminum hydride (800 mg, 21.08 mmol) in several small portions. After the addition was complete, the reaction mixture was refluxed for 8 h. The mixture was then cooled and neutralized by the slow addition of 10 M aqueous NaOH. Neutralization was assumed to be complete upon the disappearance of all gray color from the solution and the appearance of a white, sticky precipitate. The mixture was then filtered through Celite and the solvent removed from the filtrate under reduced pressure. The resulting residue was then dissolved in 40 mL of acetone and filtered again through Celite. The filtrate was poured into 500 mL of diethyl ether to precipitate the product polymer as a white solid. This material was isolated by filtration, recrystallized from 2-propanol, and dried under vacuum to yield 9.52 g (99%) of the product **11**: ¹H NMR (CDCl₃) δ 2.75 (br s, 2H), 3.28−3.85 (PEG, 440H), 4.13 (t, 2 H), 4.60 (s, 4H), 6.81 (s, 2H), 6.95 (s, 1H).

Synthesis of MeO-PEG$_{5000}$-Dibromide (12). A solution of **11** (18.0 g, 7.2 mmol) in 90 mL of methylene chloride was cooled to 0 °C. Triethylamine (3.01 mL, 21.6 mmol) was added and the solution was stirred at 0 °C for 10 min. Then, methane sulfonyl chloride (1.66 mL, 21.6 mmol) was added to the reaction solution dropwise, with stirring. The solution was stirred for an additional 20 min at 0 °C and then allowed to warm to room temperature. It was then stirred at room

temperature for 20 h. Afterward, the reaction solution was filtered through Celite and the filtrate concentrated to approximately 20 mL. The filtrate was then poured into 200 mL of diethyl ether, precipitating the product dimesylate. This material was isolated by filtration and then dissolved in 90 mL of acetone. Dry lithium bromide (2.09 g, 24.0 mmol) was added and the resulting mixture was refluxed for 21 h. The reaction solution was then filtered to remove insoluble material and the filtrate was poured into 350 mL of diethyl ether, precipitating the product. This material was filtered, recrystallized from 2-propanol, and dried under vacuum, yielding 16.4 g (91%) of the PEG-dibromide **12**: ¹H NMR (CDCl₃) δ 3.28−3.85 (PEG, 440H), 4.17 (t, 2H), 4.41 (s, 4H), 6.85 (s, 2H), 6.99 (s, 1H).

Synthesis of MeO-PEG$_{5000}$-oxy-SCS Ligand (13). A solution of thiophenol (0.986 mL, 9.60 mmol) in dry, freshly distilled THF was prepared. To this solution was added potassium *tert*-butoxide (1.33 g, 9.62 mmol). A white precipitate formed instantly. The resulting mixture was stirred at room temperature for 45 min. Then the solvent was removed under reduced pressure and the residual powdery salt was redissolved in 10 mL of DMF. This solution was then added to a solution of PEG-dibromide (**12**; 5.0 g, 2.0 mmol) in 50 mL of DMF in one portion. The resulting homogeneous solution was stirred at 75 °C for 14 h. The reaction solution was then concentrated under reduced pressure. This concentrated solution was poured into 250 mL of diethyl ether, precipitating the product. This material was isolated by filtration, recrystallized from 2-propanol, and dried under vacuum, yielding 5.0 g (>99%) of the PEG-SCS ligand **13**: ¹H NMR (CDCl₃) δ 3.28−3.85 (PEG, 440H), 3.85 (t, 2H), 4.01 (s, 4H), 6.71 (s, 2H), 6.82 (s, 1H), 7.12−7.24 (m, 10 H).

Synthesis of MeO-PEG$_{5000}$-oxy-SCS−PdCl (14). A solution of **13** (100 mg, 0.02 mmol) in 3 mL of CH₃CN was prepared in an oven-dried flask. The flask was connected to a condenser and the system sealed. The air in the system was removed by vacuum and replaced with dry N_2 and the system was allowed to purge with N_2 for 30 min. Three pump/purge cycles were performed. Then, Pd(PhCN)₂Cl₂ (7.6 mg, 0.02 mmol Pd) was quickly added to the flask. The reaction mixture was allowed to stir for 1 h at room temperature and then refluxed for 14 h. The reaction solution was then cooled and poured into 10 mL of diethyl ether, precipitating the product as a slightly golden yellow solid. This material was isolated by centrifugation, recrystallized from 2-propanol, and dried under vacuum, yielding 100 mg (>99%) of **14**: ¹H NMR (CDCl₃) δ 3.28−3.85 (PEG, 440H), 4.05 (t, 2H), 4.50−4.59 (br s, 4 H), 6.59 (s, 2H), 7.33−7.38 (m, 6H), 7.78−7.82 (m, 4H).

General Procedure for Using 14 in Homogeneous Heck Reactions. The procedure for using **14** in homogeneous Heck reactions was analogous to that previously described for **6**. The products were isolated in 71 to >99% yield and were pure by ¹H and ¹³C NMR spectroscopy.

Synthesis of 3,5-Bis(phenylthiomethyl)aniline (15). To a solution of **5** (0.487 g, 1.25 mmol) in 15 mL of 95% EtOH was added NaOH (0.150 g, 3.75 mmol). This mixture was refluxed for 20 h. Afterward, the reaction solution was neutralized with concentrated HCl and the majority of the solvent removed under reduced pressure. The remaining residue was taken up in methylene chloride. The resulting solution was washed with saturated Na₂CO₃ (3 × 15 mL) and then dried over MgSO₄. The solvent was removed under reduced pressure and the resulting oily residue was recrystallized from cyclohexane/THF to yield 0.398 g (92%) of a yellow crystalline material: ¹H NMR (CDCl₃) δ 3.59 (br s, 2H), 3.94 (s, 4H), 6.49 (s, 2H), 6.62 (s, 1H), 7.10−7.19 (m, 2H), 7.20−7.29 (m, 8H).

Synthesis of *N*-(3,5-Bis(phenylthiomethyl))phenylglutaramide (Monoamide) (16). To a solution of **15** (0.371 g, 1.10 mmol) in dry, freshly distilled THF was added glutaric anhydride (0.125 g, 1.10 mmol) and triethylamine (0.209 mL, 1.50 mmol). The resulting solution was refluxed for 30 h. After cooling, the THF was removed under reduced pressure. The residue was taken up in 20 mL of ethanol and 2 mL of 8 M NaOH was added. The solvent was then removed under reduced pressure, yielding an off-white solid material. This solid was washed with diethyl ether (3 × 40 mL) and then added to 5 mL of 6 N HCl. The solution was then extracted with methylene chloride (2 × 50 mL). The organic extracts were dried over MgSO₄ and filtered, and the solvent was removed from the filtrate under reduced pressure. The

isolated white solid product was then dried under vacuum to yield 0.438 g (92%) of the product **16**: ^{1}H NMR (CDCl$_3$) δ 2.03 (m, 2H), 2.43 (t, 2H), 2.49 (t, 2H), 4.03 (s, 4H), 6.97 (s, 1H), 7.17−7.24 (m, 10H), 7.36 (s, 1H), 7.39 (s, 2H); ^{13}C NMR (CDCl$_3$) δ 20.36, 32.72, 36.11, 38.68, 118.90, 125.19, 126.37, 128.87, 129.69, 136.05, 137.99, 138.69, 170.80, 177.74.

Palladation of *N*-(3,5-Bis(phenylthiomethyl))phenylglutaramide (Monoamide) (17). A solution of **16** (0.310 g, 0.687 mmol) in 8 mL of acetonitrile was prepared in an oven-dried flask. The flask was connected to a condenser and the system sealed. The oxygen in the system was removed with a vacuum pump and replaced with dry N$_2$; the system was allowed to purge with nitrogen for 20 min. Three pump/ purge cycles were performed. Then, Pd(PhCN)$_2$Cl$_2$ (0.263 g, 0.687 mmol) dissolved in 2 mL of CH$_3$CN was added via syringe. The resulting solution was stirred for 1 h at room temperature and then refluxed for 14 h. The reaction solution was filtered while hot to remove any insoluble material. Upon cooling, yellow crystals of pure **17** formed from the solution; the mixture was cooled at 0 °C for several hours to induce further crystallization. Finally, the product was isolated by filtration and dried under vacuum to yield 0.394 g (97%) of the product **17**: ^{1}H NMR (DMSO-d_6) δ 1.76 (m, 2H), 2.25 (t, 2H), 2.29 (t, 2H), 4.78 (s, 4H), 7.26 (s, 2H), 7.45 (m, 6H), 7.81 (m, 4H), 9.80 (s, 1H); ^{13}C NMR (DMSO-d_6) 20.45, 32.91, 35.34, 49.80, 113.22, 129.44, 129.60, 130.65, 132.24, 136.30, 149.90 (C−Pd), 170.58, 174.14; HRMS m/z 556.0232 (calcd for C$_{25}$H$_{24}$NO$_3$S$_2$Pd (M−Cl) 556.0230 (0.35 ppm error)). Selected crystallographic data for **17** are given in Table 3. Detailed X-ray crystallographic tables of **17** are available as Supporting Information.

Synthesis of MeO-PEG$_{5000}$-amido-SCS−PdCl (18). To a solution of **17** (0.118 g, 0.200 mmol) in 5 mL of DMF was added dicyclo- hexylcarbodimide (41.2 mg, 0.200 mmol). This solution was stirred at room temperature for 1 h. Then, a solution of amine-terminated PEG (1.02 g, 0.204 mmol; prepared using a previously reported procedure[23]) in 5 mL of DMF was added to the first solution in one portion. The resulting homogeneous solution was stirred at room temperature for 14 h. After the reaction, the solution was poured into 50 mL of diethyl ether, yielding a slightly pale yellow solid. This solid was collected by filtration and digested in 15 mL of methylene chloride. The insoluble urea byproduct was removed by filtration. The filtrate was poured into 75 mL of diethyl ether, precipitating the pure polymer product as a faintly yellow solid. This material was filtered, recrystallized from excess 2-propanol, and dried under vacuum to yield 1.00 g (98%) of the product **18**: ^{1}H NMR (CDCl$_3$) δ 2.15 (m, 2H), 2.31 (t, 2H), 2.79 (t, 2H), 3.38 (t, 2H), 4.62 (s, 4H), 5.42 (t, 1H), 6.71 (s, 2H), 7.40 (m, 6H), 7.82 (m, 4H).

General Procedure for Using 18 in Homogeneous Heck Reac- tions. A solution of the aryl iodide (10.0 mmol), olefin (15.0 mmol), triethylamine (15.0 mmol), and the catalyst **18** (50 mg, 0.1 mol %) in 8 mL of DMF was heated at 115 °C under an air atmosphere. The reaction progress was monitored by GC. After the reaction (2.5 or 6.5 h for **7a** and **7k**, respectively), the solution was poured into 30 mL of diethyl ether, precipitating the catalyst as a pale yellow solid. This

Table 3. Summary of Crystal Data, Details of Intensity Collection, and Least-Squares Refinement Parameters for **17**

empirical formula	C$_{28}$H$_{24}$ClNO$_3$PdS$_2$·^{3}/$_2$CH$_3$CN
M_r	690.07
crystal size, mm	0.10 × 0.30 × 0.30
crystal class	monoclinic
space group	$P2_1/n$
temp, K	193(2)
a, Å	5.6046(11)
b, Å	30.464(6)
c, Å	17.146(4)
β, deg	97.295(19)
V, Å^3	2903.8(10)
Z	4
D_{calc}, g cm^{-3}	1.451
μ(Mo Kα), cm^{-1}	90.40
$F(000)$	1284
ω scan width, deg	0.69
range Θ collected, deg	2.34−24.99
no. of independent reflcns	5078
no. of obsd data [$I > 2\sigma(I)$]	3841
R_1 [$I > 2\sigma(I)$]^a	0.0609
wR_2 (all data)	0.1641
goodness of fit	1.178
no. of parameters refined	359
max peak in final ΔF map, eÅ^{-3}	1.050

^{a} Definition of R indices: $R_1 = \sum(F_o - F_c)/\sum(F_o)$; w$R_2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.

material was washed with further portions of diethyl ether, and the washes combined with the initial filtrate. The catalyst was redissolved in DMF for use in the next cycle. The combined ether phases were washed several times with water (to remove traces of salt byproduct) then dried over MgSO$_4$. After filtration and removal of the solvent, the product was dried under vacuum. Three cycles were run for each reaction, achieving isolated yields of 85%, 87%, and 95% for **7a** and 91%, 95%, and 92% for **7k**. The isolated products **7a** and **7k** are known compounds.[28]

Supporting Information Available: Tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths, and angles, and anisotropic thermal parameters for **17** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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