JOC The Journal of Organic Chemistry

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4,4′,4″-Trimethyl-2,2′:6′,2″-terpyridine by Oxidative Coupling of 4-Picoline

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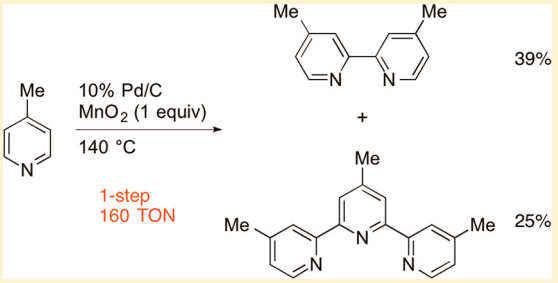
Supporting Information

ABSTRACT: Alkylated terpyridine ligands are an increasingly important component of catalysis and dyes but are costly because their synthesis is challenging and often low-yielding. We report an improved method for the Pd/C-catalyzed dehydrogenative coupling of 4-picoline to form the bi- and terpyridine. The addition of MnO_2 improves the yield of the reaction, making the reaction useful on a large scale (up to 200 mmol). The use of $Pd(OAc)_2$ or Pd/C/pivalic acid leads to the selective formation of bipyridine.



Although terpyridines are increasingly used in catalysis and in light-harvesting materials, their synthesis remains challenging.[1] For example, 4,4′,4″-trimethylterpyridine (**1a**) has found use as a ligand in dye-sensitized nanocrystalline solar cells[2] and as a precursor for bisterpyridylalkanes (Figure 1).[3] It

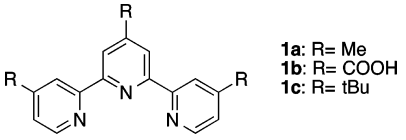


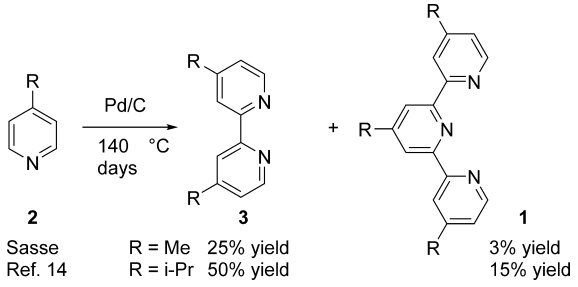
Figure 1. Terpyridine ligands.

is also a precursor to the tricarboxylate (**1b**),[4] which has also proven to be useful in dye-sensitized solar cells.[5] In addition, commercially available tri-*tert*-butylterpyridine **1c** was shown by Vicic to be a useful ligand for forming Csp^3–Csp^3 bonds in Negishi cross-coupling,[6] and we found it to be useful in reductive cross-electrophile coupling.[7] On the other hand, most terpyridines are costly and only available in small quantities (1–5 g).[8] For example, ligand **1c** is only available from one large chemical supplier,[9] and at times it has been back ordered for months. We had previously used the procedure of Ben Hadda and Le Bozec to synthesize **1c**[10] but found the yields to be variable. Herein, we demonstrate a reliable, scalable procedure for the synthesis of **1a** and demonstrate that it is a reasonable replacement for **1c** in cross-electrophile coupling.

Most methods for the synthesis of terpyridines require functionalization of the starting pyridine, adding several steps for each ligand. Condensation to form one or more of the pyridyl groups,[1a,11] cross-coupling of 2-pyridylmetal reagents with 2,6-dihalopyridines,[12] and C–H arylation of pyridine and bipyridine *N*-oxides with 2-halopyridines have all been reported.[13]

The most direct route to 4,4′,4″-trisubstituted terpyridines is the dehydrogenative trimerization of alkylpyridines (Scheme 1), first reported by Rosevear and Sasse. They found that a number of alkylpyridines, when refluxed in the presence of

Scheme 1. Previous Reports on Dehydrogenative Coupling of Alkylpyridines



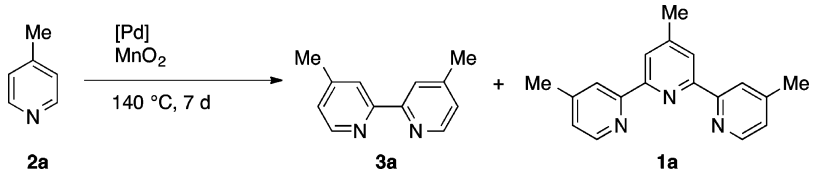
palladium on carbon (Pd/C), gave mixtures of the corresponding bipyridines (10–50% yield) and terpyridines (0.5–15% yield).[14] The highest yield was reported with 4-isopropylpyridine. Based on this work, Ben Hadda and Le Bozec developed their synthesis of **1c** from 4-*tert*-butylpyridine.[10] Further effort on developing this reaction has focused on improving the yield of bipyridine and the range of functional groups tolerated.[15] Recent studies by Åkermark and Hagelin-Weaver demonstrated that a terminal oxidant is needed[16] and that air can serve as the oxidant.[17] Bipyridines, but not terpyridines, can also be made using nickel catalysis.[18]

Our goal was to develop a one-step synthesis of a trialkylterpyridine ligand that would scale and had the potential to be low cost. We chose to focus on terpyridine **1a** due to its expected electronic similarity to **1c**, the lower cost of 4-picoline compared to 4-*tert*-butylpyridine,[19] and the established utility of

Received: August 19, 2014
Published: October 24, 2014

   dx.doi.org/10.1021/jo501925s | J. Org. Chem. 2014, 79, 10624–10628

Table 1. Optimization of Reaction Conditions



entry[a]	[Pd] source	[Pd] (mol %)	MnO_2 (equiv)	remaining **2a** (%)	yield of **3a** (%)	yield of **1a** (%)	TON[b]	**3a**:**1a**[c]
1	10% Pd/C	0.18	0.25	81	18	1	111	26.9
2	10% Pd/C	0.18	0.5	73	26	1	156	35.1
3	10% Pd/C	0.18	1.0	61	38	3	244	19.1
4	10% Pd/C	0.18	2.0	64	28	1	167	28.3
5	10% Pd/C	0.37	0.5	48	43	6	149	11.7
6	10% Pd/C	0.73	0.5	31	27	10	64	4.0
7[d]	10% Pd/C	0.73	1.0	6	56	29	156	2.9
8	10% Pd/C	0.73	0	78	11	0	15	NA
9	10% Pd/C	0	1.0	95	0	0	NA	NA
10[d,e]	10% Pd/C	0.73	1.0	2	53	30	155	2.6
11[e,f]	*10% Pd/C*	*0.75*	*1.0*	*9*	*46 (39)*[f]	*37 (25)*[f]	*160*	*1.9*
12[d]	30% Pd/C	2.19	1.0	74	14	3	9	7.3
13[e]	$Pd(OAc)_2$	3.0	1.0	30	50	1	17	98.4
14[e,g]	10% Pd/C	0.73	1.0	38	51	0	70	NA

[a]Reaction set up in glovebox in 1-dram vial with 20.55 mmol of 4-picoline, Pd/C, and MnO_2. This vial was sealed and stirred at 140 °C for 7 d. Yields are corrected GC yields vs dodecane as an internal standard. Isolated yields in parentheses. [b]Turnover number calculated as number of C−C bonds formed/Pd atom. [c]The ratio of **3a** to **1a**, not the ratio of yields of **3a** to **1a**. For example, 50% yield of **3a** and a 50% yield of **1a** would yield 5.14 mmol of **3a** and 3.43 mmol of **1a**; thus, the ratio of **3a**:**1a** would be 1.5:1. [d]Ran for 6 days. [e]Set up using an oven-dried vial on the benchtop. [f]Used 1.95 mL (20 mmol) of 4-picoline. [g]With 20 mol % of 2,2-dimethylpropionic acid.

1a in light harvesting. Unfortunately, the highest reported yield for the dehydrogenative synthesis of **1a** from 4-picoline was 3% (Scheme 1).[14]

In preliminary studies, the major challenges were low conversion of picoline and a high ratio of bipyridine (**3a**) to our desired terpyridine (**1a**). In order to improve the turnover numbers of the catalyst, we sought a chemical oxidant to regenerate palladium(II) oxide, since oxidants are typically required for dehydrogenative coupling reactions.[20] Although Hagelin-Weaver found that air was suitable for their catalysts,[17] we did not see any improvement in yields with commercial Pd/C. A variety of solid oxidants were tested ($CuCl_2$,[21] $FeCl_3$, benzoquinone,[22] DDQ, and Oxone[23]), but only unactivated MnO_2 was found to produce significant yields of terpyridine **1a** and bipyridine **3a** (Table 1), which we attribute to the reoxidation of Pd(0) to Pd(II). While activated MnO_2 is known to oxidize Pd(0) to Pd(II),[24] use of commercial activated MnO_2 in this procedure yielded only starting material.[25] Increasing the oxidant loading to 1 equiv increased the turnover number (TON) and slightly improved the ratio of **3a**:**1a** (entries 1−3). Beyond 1 equiv, yields dropped as stirring the solution became difficult (entry 4). Further improvements in the conversion of picoline to coupled products and the ratio of **3a**:**1a** were obtained by increasing the catalyst loading (entry 2 vs entries 5 and 6).

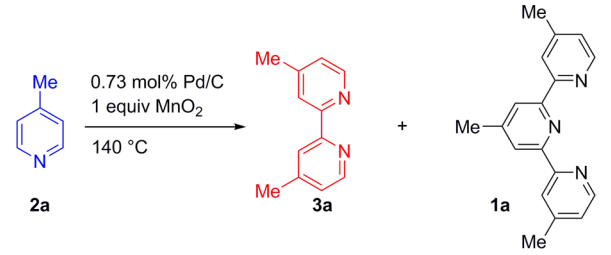
These two effects were cumulative, and reaction of picoline with 1 equiv of MnO_2 at a loading of 0.73 mol % of Pd resulted in nearly complete conversion and a 2.9:1 ratio of **3a**:**1a** (entry 7). The same reaction conducted without MnO_2 provided no terpyridine and only a small amount of bipyridine (entry 8), confirming the positive role of the oxidant. Similarly, Pd is required for coupling to occur (entry 9). The reaction could be set up on the benchtop, as long as all materials were rigorously dry (entries 10 and 11), and the products could be isolated by sublimation in reasonable yield. The remaining material contained higher oligopyridines up to the sexipyridine (determined by LC−MS analysis).

Most of the other Pd sources we tested[26] were found to be unsuitable catalysts with two exceptions: 30% Pd/C (entry 12) and $Pd(OAc)_2$ (entry 13). Although $Pd(OAc)_2$ is a well-known catalyst for the oxidative coupling of arenes and C−H functionalization,[20] in our reactions Pd metal precipitates within the first few hours. Even after this plating out, however, product continues to be formed. For both the Pd/C- and the $Pd(OAc)_2$-catalyzed reactions, it is unclear whether heterogeneous catalysis, as suggested by Hagelin-Weaver's work,[16,17] or homogeneous catalysis[20] is at work. The $Pd(OAc)_2$-catalyzed reaction was highly selective for bipyridine formation (**3a**), which was different from the Pd/C-catalyzed reactions (entry 13 vs entries 1−12). However, a similar selectivity was observed when 2,2-dimethylpropionic acid was added to a reaction catalyzed by 10% Pd/C (entry 14), suggesting that the carboxylate ligands alter the selectivity and that the two catalysts operate in a similar fashion.

A study of the amount of product formed over time (Figure 2) shows that bipyridine is produced continuously until day 4 or 5 and terpyridine production is minimal until about day 4. We found that the addition of bipyridine **3a** does not significantly increase the amount of terpyridine **1a** produced, consistent with the observation of Sasse.[14] At this time, it is unclear why a mixture of **2a** and **3a** does not produce more **1a**.

To test the scalability of this heterogeneous reaction, we conducted a synthesis of **1a** from 19.5 mL (200 mmol) of 4-picoline (**2a**) on the benchtop using a mechanical stirrer, a three-neck flask, and a reflux condenser (Scheme 2). The reaction scaled well, affording gram quantities of **1a** and **3a** in a single step, albeit with a long reaction time.

dx.doi.org/10.1021/jo501925s | J. Org. Chem. 2014, 79, 10624−10628



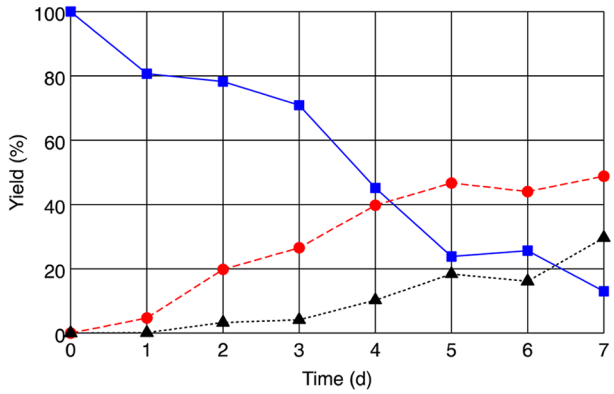
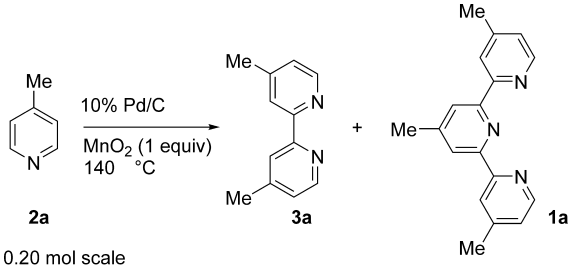


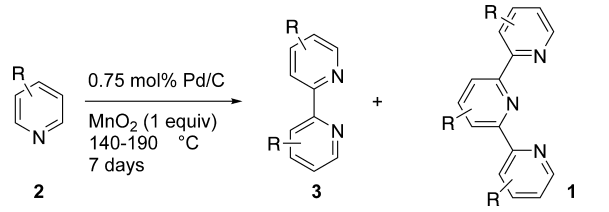
Figure 2. Bipyridine and terpyridine formation over time. Legend: **2a** (blue boxes, solid line), **3a** (red circles, dashed line), and **1a** (black triangles, dotted line). Procedure: 12 reactions were set up according to Table 2, entry 8. Each day, two reactions were halted, except days 6 and 7, where one reaction was halted.

Scheme 2. Large-Scale Synthesis of Trimethylterpyridine 1a



We also briefly examined the substrate scope of this procedure. Overall, the scope is promising and improved compared to literature reports, but conversions, selectivities, and yields were not as high as with 4-picoline (Table 2). As expected, 3-picoline only produced trace amounts of terpyridine **2d**, but a 31% isolated yield of bipyridine **3d** was obtained. This compares favorably with the literature yields of 36% (Raney Ni)[27] and 0.5% (Pd/C).[28] The reaction of the electron-rich pyridine, 4-(dimethylamino)pyridine (**2f**), afforded a 40% yield of bipyridine **3f** along with a 16% yield of terpyridine **1f**. While the synthesis of bipyridine **3f** by ruthenium catalysis[29] is known in 32% yield, trimerization to form **1f** has not been previously reported. The slightly electron withdrawing 4-phenylpyridine (**2e**) (Table 2, entries 2 and 3) could be dimerized to **3e** in 49% yield along with an 11% yield of the known terpyridine **1e**,[30] but more electron-poor pyridines were largely unreactive. The dimerization of 4-phenylpyridine to bipyridine **3e** over Raney Ni was previously reported in 5% yield,[27] but the trimerization has not been reported. Finally, we found 4-*tert*-butylpyridine **2c** to be relatively unreactive for reasons we are unable to explain at this time (entry 4). As an alternative, a reasonable yield of 4,4′-bis(trimethylsilyl)-2,2′-bipyridine (**3g**) could be obtained (entry 5). The only previous synthesis of this bipyridine was from the dibromobipyridine in 12% yield.[31] Due to the moderate selectivity and conversions obtained in entries 2−4, we did not isolate the products of these reactions.

Table 2. Substrate Scope



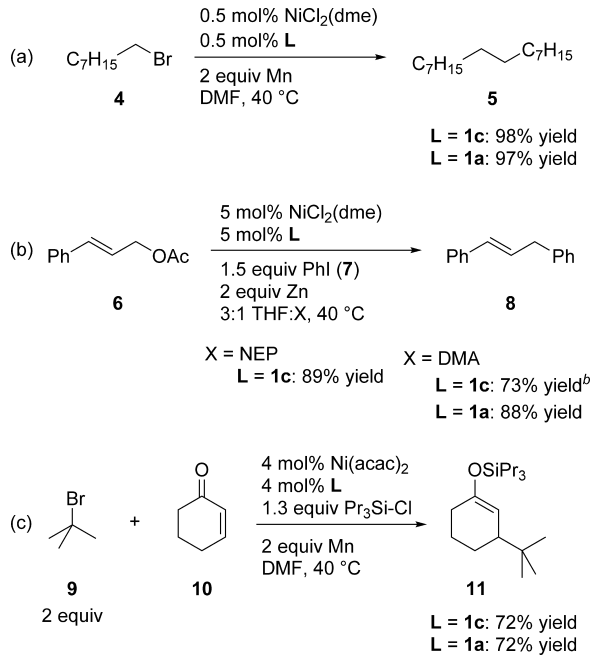
entry[a]	substrate	**2** (%)	yield of **3** (%)	yield of **1** (%)	**3**:**1**
1[b,c]	R = 3-Me, **2d**	34	53 (31)	1	53:1
2[d,e]	R = 4-Ph, **2e**	22	49	11	4.5:1
3[d]	R = 4-NMe_2, **2f**	40	40	16	2.5:1
4[f]	R = 4-*t*-Bu, **2c**	91	8	0.7	11:1
5	R = 4-$SiMe_3$, **2g**	30	42 (42)	2	21:1

[a]Set up on the benchtop in an oven-dried 1-dram vial with substrate, 0.75 mol % of 10% Pd/C, and 100 mol % of MnO_2 at 190 °C. Yields are assay yields based upon GC areas % data. Isolated yields are given in parentheses. [b]Corrected GC yield. [c]Run at 140 °C. [d]Yield determined by ^{1}H NMR. [e]Average of 2 runs. [f]1.5 mol % Pd/C was used.

Finally, we tested **1a** as a replacement for **1c** in our published cross-electrophile coupling reactions (Scheme 3). In each case, reactions with **1a** provided results equal to or better than our published results.[7]

In summary, an economical, one-step method to make 4,4′,4″-trimethyl-2,2′:6′,2″-terpyridine (**1a**) has been developed. The use of MnO_2 as an oxidant was found to dramatically

Scheme 3. Performance of 1a in Reductive Cross-Electrophile Coupling Reactions[a,b]



[a]Yields are isolated yields of purified product. [b]From ref 7c, GC yield, corrected.

dx.doi.org/10.1021/jo501925s | J. Org. Chem. 2014, 79, 10624−10628

increase the conversion of the oxidative coupling and enhance the amount of terpyridine produced, while an increased catalyst loading further improved the ratio of terpyridine to bipyridine. Unactivated MnO_2 was the only oxidant studied that improved TON and it might prove generally useful in other palladium-catalyzed oxidative chemistry.[20,24] Finally, ligand **1a** is a suitable replacement for **1c** in cross-electrophile and dimerization chemistry, suggesting that **1a** will be generally useful in catalysis.

EXPERIMENTAL SECTION

General. MnO_2 (>99%, *not* "activated" grade) and palladium on carbon (Pd/C) (10 wt %, matrix carbon, dry support, Sigma-Aldrich) were used as received. 4-Picoline was distilled from KOH prior to use. 4-(Trimethylsilyl)pyridine (**2g**) was prepared according to the literature procedure.[32]

Methods. NMR chemical shifts are reported in ppm, referenced to the residual solvent peak of $CDCl_3$ (δ= 7.26 ppm for ^1H or δ = 77.16 ppm for ^{13}C) as an internal standard, and J values are given in hertz. NMR spectra were recorded at 400.13 or 500.13 MHz proton NMR frequency. GC analyses were performed on a DB-5 column (20 m × 180 μm × 0.18 μm) with an FID detector, and with H_2 as carrier gas. General method: 1 μL injection of sample, injection temp of 300 °C, 100:1 split ratio, and initial inlet pressure was 20.3 psi but varied as the column flow was held constant at 1.8 mL/min for the duration of the run. Initial oven temperature of 50 °C was held for 0.46 min followed by a temperature ramp up to 300 °C at 65 °C/min, and finally the temperature was held at 300 °C for 2.69 min. Total run time was ∼7 min. FID temperature was 325 °C. Chromatography was performed on SiO_2 (silica gel 60, particle size 0.040−0.063 mm) using standard flash techniques. Products were visualized by either UV light or phosphomolybdic acid.

General Procedures. General Procedure A: Glove Box. Inside a nitrogen glovebox, a 1-dram vial was charged with 10% Pd/C (160 mg, 0.73 mol %), MnO_2 (1.79 g, 20.6 mmol), 4-picoline (2.00 mL, 1.91 g, 20.6 mmol), and a polytetrafluoroethylene-coated (PTFE) magnetic stirbar. The vial was then capped with a screw cap fitted with a PTFE-faced silicone septum, removed from the glovebox and then shaken for 15 s before being stirred (1200 rpm) at 140 °C for 7 d. After 7 d, the reaction mixture was carefully opened and poured hot into a 20 mL scintillation vial. The 1 dram vial was washed multiple times with CH_2Cl_2 (∼15 mL in total), and these washings were added to the scintillation vial, along with any remaining solids. The resulting mixture was sonicated for 15 min to ensure all soluble materials were fully dissolved before it was filtered through a plug of diatomaceous earth (1 in. wide, ∼1 in. high) in an 18 mL disposable polyethylene fritted filter funnel. The diatomaceous earth pad was washed with ∼10 mL CH_2Cl_2. Samples from this mixture were used for GC analysis. **General Procedure B: Benchtop.** As procedure A, except the reaction as set up on the benchtop with no precautions to exclude air. However, to exclude moisture, oven-dried glassware was used. **General Procedure C: Isolated Yield.** As procedure B, except ∼100 mL of CH_2Cl_2 was used in filtration, and 159.6 mg of 10% Pd/C (0.75 mol %), 1.74 g of MnO_2 (20 mmol), and 1.95 mL of 4-picoline (1.86 g, 20 mmol) were used.

*4,4′-Dimethyl-2,2′-bipyridine (**3a**) (CAS No. 1134-35-6).*[33] General procedure C was followed. The crude solid was purified by sublimation (150 °C/20 mTorr, 36 h). The sublimate was removed from the coldfinger and sublimed again (100 °C/20 mTorr, 8 h). The sublimate of this second sublimation was a white solid whose spectra matched the literature for **3a** (0.71 g, 3.85 mmol, 39% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 8.54 (d, J = 4.9 Hz, 2H), 8.23 (s, 2H), 7.13 (d, J = 4.6 Hz, 2H), 2.44 (s, 6H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 156.0, 148.9, 148.1, 124.6, 122.0, 21.2. Compound **3a** was purified further by recrystallization in ethyl acetate (recrystallized yield 0.40 g, 2.16 mmol, 22% yield). Mp: 166−171 °C (lit.[32] mp 171.9−172.4 °C). Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 77.88; H, 6.52; N, 14.96

*4,4′,4″-Trimethyl-2,2′:6′,2″-terpyridine (**1a**) (CAS No. 33354-75-5).*[12a] The white material remaining after the second sublimation of **3a** was pure **1a** (0.47 g, 1.69 mmol, 25% yield). The ^1H NMR spectrum was in good agreement with the literature report. The ^{13}C NMR spectrum was consistent with the structure and the symmetry of **1a** but did not match the spectrum previously reported (ref 12a contains an extra peak at 123.5 ppm and is missing the peak at 149.1 ppm). Mp: 180−182 °C (lit.[12a] 186 °C). ^1H NMR (500 MHz; $CDCl_3$): δ 8.59 (d, J = 5.0 Hz, 2H), 8.44 (s, 2H), 8.30 (s, 2H), 7.18 (d, J = 5.1 Hz, 2H), 2.55 (s, 3H), 2.53 (s, 6H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 156.2, 155.5, 149.1, 148.9, 148.0, 124.7, 122.08, 122.02, 21.38, 21.35. Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.18; H, 6.24; N, 15.12.

Large-Scale Procedure. *200 mmol Scale.* While hot, a reflux condenser, mechanical stirring rod, and plug were attached to a three-neck round-bottom flask. A N_2 inlet and outlet were then attached to the reflux condenser, and the apparatus was cooled under N_2. The stirring rod was then attached to an air-powered mechanical stirrer. Pd/C (10%, 1.60 g, 0.75 mol %), MnO_2 (17.4 g, 200 mmol), and 4-picoline (**2a**) (19.5 mL, 200 mmol, distilled over KOH) were added to the apparatus under positive N_2 pressure while stirring. This mixture was then heated to reflux. After 7 days, 25 mL of mesitylene was added to the mixture, and then the mixture was allowed to cool. This mixture was filtered through a 150 mL course frit with 1 in. of diatomaceous earth on top of 2 cm of sand with 1 L of CH_2Cl_2. The CH_2Cl_2 was removed by rotary evaporation, and the remaining **2a** and mesitylene was removed on a high-vacuum line (∼50 mTorr).

*4,4′-Dimethyl-2,2′-bipyridine (**3a**) (CAS No. 1134-35-6).*[32] The crude solid was sublimed for 15 h (100 °C/50 mTorr). The sublimate was isolated as a white solid whose spectra matched the literature spectra for **3a** (7.38 g, 40.1 mmol, 40% yield).

*4,4′,4″-Trimethyl-2,2′:6′,2″-terpyridine (**1a**) (CAS No. 33354-75-5).*[12a] The solid remaining after the sublimation above was then sublimed for 21 h (135 °C/50 mTorr). The sublimate was isolated as a white solid whose spectra matched the literature spectra for **1a** (2.61 g, 9.48 mmol, 14% yield).

*5,5′-Dimethyl-2,2′-bipyridine (**3b**) (CAs No. 1762-34-1).*[32] General procedure C was employed with 3-picoline (**2b**) (1.95 mL, 20 mmol). Two 20 mmol runs were combined for purification and isolation. After 7 days, the remaining starting material was removed by rotary evaporation, and then the crude solid was purified by sublimation (80 °C/20 mTorr, 12 h). The sublimate was isolated as a light brown solid whose spectra matched the literature spectra for **3b** (1.12 g, 31% yield overall). Mp: 108−112 °C (lit.[32] mp 113.7−114.1 °C). ^1H NMR (400 MHz; $CDCl_3$): δ 8.48 (s, 2H), 8.23 (d, J = 8.1 Hz, 2H), 7.59 (dd, J = 8.0, 1.6 Hz, 2H), 2.37 (s, 6H). ^{13}C NMR (126 MHz; CDCl3): δ 153.8, 149.5, 137.4, 133.0, 120.3, 18.4. Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 77.76; H, 6.53; N, 15.03.

*4,4′-Bis(trimethylsilyl)-2,2′-bipyridine (**3g**) (CAS No. 372805-52-1).* General procedure C was followed with 4-(trimethylsilyl)pyridine (**2g**) (0.48 g, 3.2 mmol) using 280 mg MnO_2 (3.2 mmol) and 25.6 mg 10% Pd/C (0.75 mol %). After 7 days, the remaining starting material was evaporated and the crude solid was purified by sublimation (120 °C/70 mTorr, 1 h) to afford the product as an off-white solid (0.20 g, 42% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 8.65 (d, J = 4.7 Hz, 2H), 8.48 (s, 2H), 7.41 (d, J = 4.7 Hz, 2H), 0.34 (s, 18H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 155.2, 151.3, 148.0, 128.1, 125.7, −1.6.

*Hexadecane (**5**) (CAS No. 544-76-3).* Product **5** was prepared according to the literature procedure on a 2 mmol scale except that ligand **1a** was utilized in place of **1c**. Hexadecane (226 mg, 100% yield) was isolated as a clear liquid whose spectra matched those reported. The reaction was repeated, and 215 mg (95% yield) of **5** was obtained.

*(E)-Prop-1-ene-1,3-diyldibenzene (**8**) (CAS No. 3412-44-0).*[7c] Product **8** was prepared according to the literature procedure except that ligand **1a** was utilized in place of **1c**. After purification by column chromatography (100% pentane), 171 mg (88% yield) of **8** was isolated as a clear liquid. Spectra matched those previously reported in the literature.

dx.doi.org/10.1021/jo501925s | J. Org. Chem. 2014, 79, 10624−10628

*[(3-tert-Butylcyclohex-1-en-1-yl)oxy]tripropylsilane (**11**) (CAS No. 1286212-20-1).*[76] Product **11** was prepared according to the literature procedure on a 1.00 mmol scale except that ligand **1a** was utilized in place of **1c**. The compound was isolated as a clear liquid (223 mg, 72% yield) whose spectra matched the literature report.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NIH (R01 GM097243). We acknowledge additional support from the Department of Education (MRP, GANN Grant No. P200A120011), NSF (MTR, REU program CHE-1156340 and CHE-0849892), and the University of Rochester (MTR, Portable Research Grant). D.J.W. is an Alfred P. Sloan Research Fellow and a Camille Dreyfus Teacher−Scholar. Analytical data were obtained from the CENTC Elemental Analysis Facility at the University of Rochester, funded by NSF CHE-0650456. LC−MS instrumentation was supported by the NSF Grant No. CHE-0946653. We thank Nicolas J. Gower and Don Batesky (University of Rochester) for experimental advice.

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