A Practical Synthesis of *trans*-Dichlororuthenium ((*S,S*)-2,6-Bis(4-isopropyl-2-oxazolin-2-yl)-pyridine)(ethylene) Amenable to Large-Scale Preparation

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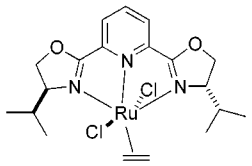
The enantioselectivity achieved using transition metal catalysts can be strongly influenced by chiral bisoxazoline ligands.[1] Catalysts such as **1**, which utilize pyridine bisoxazoline (Pybox) ligands, have garnered much attention. Pybox ligands have been employed in the preparation of chiral catalysts for asymmetric transformations such as Kharasch,[2] hydrosilylation,[3,4] aldol,[5] Diels−Alder,[6,7] and cyclopropanation[8,9] reactions. Given the utility of the Pybox ligands, it is desirable to have a safe, cost-effective process for the preparation of the necessary Pybox ligand, and the appropriate catalyst, on larger scale (≥1 kg), with reproducible yields and quality.



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Several procedures for the synthesis of Pybox ligands are reported in the literature. Singh and co-workers[2] used a methanesulfonic acid promoted dehydrative cyclization to form the oxazoline rings. However, this method requires conditions (e.g., larger solvent volumes) that may not be desirable for manufacturing. Another dehydrative cyclization approach employing BF_3·OEt_2 was reported by Davies et al.[10] The disadvantages of this process on scale are the use of the Lewis acid as the solvent and high reaction temperature (120 °C). Nishiyama[4] published a four-step procedure starting from a commercially available 2,6-pyridinedicarboxylic acid that afforded the desired Pybox ligand in a good overall yield (64%). However, the use of $SOCl_2$ (in the first step as the solvent) in two steps, 95% NaH in the oxazoline cyclization step, and silica gel chromatography of an intermediate in this process were not desirable for scale-up in a manufacturing environment.

We were able to modify Nishiyama's procedure for use in our pilot facility to produce the Pybox ligand in multikilogram quantities (Scheme 1). 2,6-Pyridinedicarbonyl chloride, **2**, was prepared by treatment of less-expensive 2,6-pyridinedicarboxylic acid[11] with excess Vilsmeier reagent in CH_2Cl_2, affording **2** in yields of >94% as determined by in-process quantitation.[12] The dicarbonyl chloride **2** was coupled with L-valinol (96%, 97% ee) under Schotten−Baumann conditions. The coupled product **3** precipitated out at the CH_2Cl_2/aqueous interface and was collected by vacuum filtration in yields of 70 to 80%. Decantation of a portion of the top aqueous phase was necessary to reduce the filtration time.[13] Experiments using higher concentrations of NaOH (having smaller aqueous volumes and, thus, shorter filtration times) gave lower yields of **3** and increased amounts of recovered 2,6-pyridinedicarboxylic acid from hydrolysis of **2**.

A THF slurry of **3** was added to Vilsmeier reagent in THF at 20 to 25 °C. Analysis by HPLC indicated that all of **3** was consumed in approximately 4 h, and that in 10 to 12 h, the dichloride **4** was the major product observed. The reaction was treated with a TEA/THF solution at −10 to 0 °C. The TEA/THF solution was added at such a rate as to maintain the −10 to 0 °C temperature range. The resultant mixture was heated to 50 °C for 1 to 1.5 h and then exchanged into toluene following aqueous workup to remove TEA·HCl. The toluene solution of **4** was treated with aqueous 40 wt % tetra-*n*-butylammonium hydroxide and 10% KI. After stirring the mixture at 30 to 35 °C for 10−12 h, Pybox **5** was obtained in yields of 71−80% after workup and crystallization. The optical rotations ranged from −110 to −117° ($c = 0.7$, CH_2Cl_2),[14] and the overall yields from 2,6-pyridinedicarboxylic acid were 53−63%. (Results of laboratory and pilot facility runs are summarized in Table 1).

Alternative routes for the synthesis of **5** were explored. Treatment of **3** with methanesulfonyl chloride and a variety of amine bases produced mixtures containing a

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(11) , 6-Pyridinedicarbonyl chloride is commercially available at ca. $4000/kg, whereas 2, 6-pyridinedicarboxylic acid is priced at $320/kg (both from Sigma-Aldrich-Fluka).
(12) A 50 μL aliquot of the reaction mixture was quenched in acetonitrile containing 1 mL of diethylamine and diluted to 10 mL. The amount of 2,6-pyridinedicarboxamide was measured by HPLC. The acid chloride preparation was deemed complete when the yield of the dicarboxamide was >90 M% (typically, it was >94 M%).
(13) Addition of seed crystals of **3** to the mixture of L-valinol, NaOH, and CH_2Cl_2 prior to acid chloride charge helps produce larger crystals of **3**, and increases the overall filtration rate.
(14) The optical rotation of a commercially available sample of **5** (Sigma-Aldrich-Fluka) was −117 ± 3° (c 0.7, CH_2Cl_2), and mp = 155−157 °C. Nishiyama reports an optical rotation of −116.8° (c 1.0, CH_2Cl_2; see ref 3b).

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Scheme 1

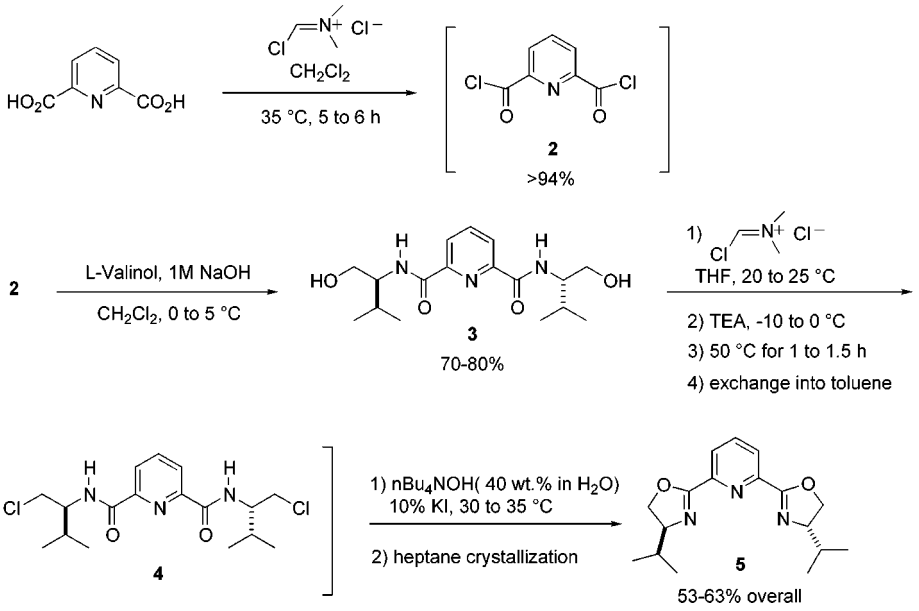

Table 1. Yields of Chiral Diol 3 and Pybox Ligand 5[a]

run	pyridine-dicarboxylic acid (kg)	yield of **3** (kg)	% yield of **3**	input **3** (kg)	yield of **5** (kg)	% yield of **5**	overall yield (%)
1	0.02	0.0321	76.5	0.02	0.0144	80.6	61.7
2	6.71	10.10	72.4	10.10	6.70	74.2	53.7
3	6.71	10.72	79.0	10.10	7.12	79.0	62.4

[a] Yields are corrected for water content.

number of unidentified impurities and low amounts of **5**. *p*-Toluenesulfonyl chloride with NMM as the base performed better, giving much cleaner reaction mixtures at 20 to 25 °C. However, after 8 days at this temperature, the conversion of **3** to **5** was not complete. Analysis of the crude reaction mixture revealed the presence of a minute quantity of **3** and a significant amount of a monooxazoline intermediate (both unquantified). Experiments run at higher temperatures proceeded at a much faster rate, but afforded only moderate yields of **5** that required treatment with activated charcoal to remove discoloration. The results of the methane and *p*-toluenesulfonyl chloride experiments question the stability of the mesylate and tosylate intermediates formed in these reactions. Attempts to form the bisoxazoline ligand by treatment of **3** with *p*-toluenesulfonic acid and azeotropic removal of water (Dean−Stark trap) yielded moderate amounts of **5** mixed with small amounts of **3**, and minute amounts of other impurities. The NMR spectrum of **5** from this method was not clean, and the mass balance was poor.

The Ru·Pybox catalyst **1** was prepared according to the literature procedure.[9b,15] The reaction is shown in Scheme 2. Dichlororuthenium(II) (*p*-cymene) dimer and **5** were dissolved in CH_2Cl_2 at 20 to 25 °C. Ethylene gas was bubbled in[16] until the reaction was complete, typically in 30 min, by NMR.[17] The catalyst was crystallized by addition of the reaction mixture to heptane. The yield of **1** after drying was 87−91% based on the input of **5**. The yields are uncorrected for residual ligand, which was

Scheme 2

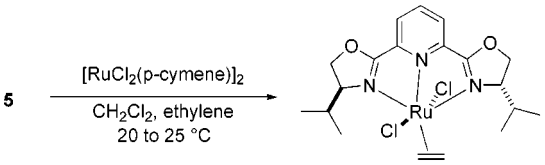

Table 2. Yields of Ru·Pybox-ip Catalyst 1[a]

run	input ligand **5** (kg)	yield of **1** (kg)	% yield of **1**
1	0.05	0.0694	83.4
2	0.75	1.06	84.8
3	0.80	1.16	85.9

[a] Yields are corrected for water content.

usually seen in 5−10 M% (this did not appear to adversely affect the activity or selectivity of the catalyst in our hands). Yields corrected for residual **5** are provided in Table 2. The main advantage in this process is the replacement of silica gel chromatography of **1** by a crystallization. The chromatography of **1** was cumbersome, even on a few grams scale. Also, the catalyst adhered to the walls of the flask on concentration, making transfer difficult. By contrast, our isolation method affords **1** as a free-flowing slurry that filters easily. The burgundy-colored catalyst is air-stable and can be stored in amber bottles at ambient temperatures for extended periods of time.

One caveat on the amount of **5** used in the preparation of **1** should be noted. When the input of **5** was over 800 g in one trial, impurities were observed in **1** that were difficult to completely purge. The reason for this is not known, and further examination is in progress.

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(16) For small scale reactions, headspace ethylene can be used without any loss of yield or quality.

(17) When the NMR shows <10% of **5**, the reaction is deemed complete. For an NMR sample: 100−200 μL of reaction mixture was removed and blown to dryness with N_2. The residue was dissolved in $CDCl_3$, and its proton spectrum was recorded. The areas under the multiplet at 1.85 ppm (isopropyl methine for the ligand) and 2.5 ppm (isopropyl methine for the catalyst) were integrated and used in the calculation for determining the amount of **5** remaining in the reaction mixture. Normally, 5−10% of free **5** is observed.

In summary, we have defined a process which allows the preparation of the chiral Pybox ligand **5** reproducibly on a >1 kg scale. The procedure circumvents processing obstacles that restrict the usage of existing methods. Although Vilsmeier reagent and tetra-*n*-butylammonium hydroxide are more expensive than $SOCl_2$ and NaH used in Nishiyama's procedure,[4] they offer improved and safer handling on kilogram scale. The chiral catalyst **1** was prepared on near kilogram scale reproducibly with good quality. Efforts to streamline this process further are underway.

Experimental Section

General. 2,6-Pyridinedicarboxylic acid, Vilsmeier reagent, L-valinol, 40 wt % tetra-*n*-butylammonium hydroxide, and potassium iodide were commercially available and used as is. Toluene, THF, and CH_2Cl_2 were used without any further purification or drying. THF was checked for peroxides prior to use with indicator strips. The moisture content of THF should be ≤0.05% w/w, and ≤ 0.01% w/w for CH_2Cl_2. Moisture content was determined by coulometric titration on a Mitsubishi CA-06 moisture meter on a weight/weight basis. Melting points were obtained using a Thomas-Hoover melting point apparatus and are uncorrected. Proton and carbon NMR were run on a Bruker AC-300 spectrometer at 300 MHz for proton and 75 MHz for ^{13}C in d_4-MeOH or $CDCl_3$. High-pressure liquid chromatography was run under the following conditions: column = YMC ODS-A, 5 μm, 150 × 4.6 mm; flow rate = 1 mL/min; detector = 250 nm; injection volume = 10 μL; column temperature = 25 °C; mobile phase = CH_3CN/H_2O (w/ 0.1% v/v TFA) according to the timetable below:

time (min)	% CH_3CN	% H_2O
0	30	70
10	30	70
20	70	30
30	70	30
35	30	70
40	30	70

The retention time is 3.8 min for **3**, 7.8 min for **5**, 20 min for toluene, and 21.4 min for **4**. Gas chromatography was done under the following conditions: column = Restek Rt-X1, 30 m, i.d. 0.32 mm; T_i = 50 °C (hold for 2 min); T_f = 200 °C (hold for 10 min); ΔT = 10 °C/min. The retention time is 2.4 min for CH_3CN, 3.7 min for THF, 4.8 min for TEA, 6.3 min for toluene. Compounds **1**[15a] and **5**[3b] have been reported in the literature.

***(S,S)*-2,6-Bis(*N*,*N*′-3-hydroxy-2-isopropyl)pyridinedicarboxamide (3).** A 500 mL, three-neck flask was equipped with a mechanical stirrer, thermocouple probe, reflux condenser, and N_2 inlet. The flask was flushed with N_2 for at least 15 min. Charge the flask with (chloromethylene)dimethylammonium chloride (Vilsmeier reagent; 40.88 g, 319.4 mmol, 2.6 equiv) and CH_2Cl_2 (200 mL). Stir the thick slurry efficiently at 20 to 25 °C, and then add solid 2,6-pyridinedicarboxylic acid (20.41 g, 122.1 mmol) in one portion under a gentle stream of N_2 (no exotherm observed).[18] Stir the resulting yellow solution at 30 to 40 °C for 5−6 h under an atmosphere of N_2.[12,19] Hold the solution of **2** for the coupling reaction (the acid chloride solution is stable enough at 20 to 25 °C to be held for 25 h without loss of potency).

A 2 L, three-neck flask was equipped with a mechanical stirrer, addition funnel, and a Claisen adapter fitted with a thermocouple probe and N_2 inlet. The flask was flushed with N_2 for 10 min. Charge the flask with L-valinol (30.56 g, 296.2 mmol, 2.4 equiv), CH_2Cl_2 (32 mL), and 1 M NaOH (733 mL, 733 mmol, 6 equiv). Cool the mixture to 0−5 °C. Charge the addition funnel with the acid chloride **2**. Add the solution of **2** subsurface over 30 to 40 min, maintaining the temperature at 0−10 °C (the addition is exothermic), and gradually increasing the rate of stirring as **2** is added. Stir the reaction at 0−10 °C for 10 min and then at 20−25 °C for 10−12 h. Cool the mixture down to 0−10 °C and hold there for 1 h. Stop the stirring, and allow the phases to separate (**3** will precipitate and reside at the aqueous/organic interface). Carefully siphon off ∼500 mL of the top aqueous layer (this reduces filtration time. See ref 13). Collect the product by vacuum filtration of the cold mixture. Wash the filter cake with cold water (50 mL) and cold CH_2Cl_2 (50 mL). Dry the wet cake at 45 to 55 °C under reduced pressure for 18 to 20 h (or until the moisture content is <1% w/w) to afford 32.1 g (76.5 M%) of **3** as a white solid. mp = 118−120 °C; moisture content = 0.8% w/w; ^1H NMR (d_4-MeOH) δ: 8.18 (d, J = 8.07 Hz, 2H), 8.05 (dd, J = 7.39. 8.79, 15.46 Hz, 2H), 3.81 (m, 2H), 3.66 (d, J = 5.13 Hz, 4H), 1.93 (m, 2H), 0.93 (d, J = 6.66 Hz, 6H), 0.88 (d, J = 6.70 Hz, 6H); ^{13}C NMR (d_4-MeOH) δ: 165.97, 150.50, 140.33, 125.98, 63.08, 58.76, 30.23, 20.19, 19.50. Anal. Calcd 60.51% C, 8.07% H, and 12.45% N for $C_{17}H_{27}N_3O_4$. Found: 60.25% C, 7.78% H, 12.37% N.

***(S,S)*-2,6-Bis(4-isopropyl-2-oxazolin-2-yl)pyridine (5).** A 1 L, three-neck flask was equipped with a mechanical stirrer, an addition funnel, and a Claisen adapter fitted with a thermocouple probe and N_2 inlet. The flask was flushed with N_2 for at least 15 min. Charge the flask with Vilsmeier reagent (19.82 g, 154.8 mmol, 2.6 equiv) and dry THF (100 mL). Stir the mixture vigorously at 20 to 25 °C. Charge a slurry of **3** (20.00 g, 59.3 mmol, 1 equiv) in dry THF (100 mL) in one portion at 20 to 25 °C (an exotherm of 10 °C was observed, but quickly drops off). Stir the reaction at 20 to 25 °C for 10 to 12 h to afford the dichloride **4**.[20] Cool the reaction to −10 to −5 °C and charge the addition funnel with TEA (50 mL, 358.7 mmol, 6 equiv) and dry THF (50 mL). Add the TEA/THF solution subsurface[21] over 15 min, maintaining the temperature at −10 to 0 °C. Replace the addition funnel with a reflux condenser and heat the reaction to 50 ± 2 °C for 1−1.5 h.[22] Cool the reaction to 20 to 25 °C and add deionized H_2O (50 mL) to dissolve TEA·HCl. Stir for 10 min, and then separate the two phases. Extract the aqueous phase with toluene (50 mL), and combine the organics. The rich organic can be held at 20−25 °C for up to 64 h without any loss in quality or yield.

Charge the rich organic to a calibrated 1 L, three-neck flask equipped with a mechanical stirrer, concentrator condenser, and a thermocouple probe. Concentrate the rich organic to 25−35% of the starting volume (final volume of ∼150 mL in this case) with moderate stirring at 40−50 °C under reduced pressure (15−20 inHg of vacuum). It is advisable to put a small amount of BHT in the receiver flask to retard peroxide formation. Cool the concentrate to 20−25 °C, and then add solid KI (0.98 g, 5.9 mmol) and a 40 wt % solution of tetra-*n*-butylammonium hydroxide in water (115.5 g of solution, 178 mmol).[23,24] Heat the biphasic mixture at 30 ± 2 °C with vigorous stirring for 10−12 h. (If the reaction stalls, an additonal charge of the base can be made to push the reaction to completion. The reaction can be left to run for up to 24 h without any loss in yield or quality). Dilute the reaction with H_2O (50 mL) and toluene (100 mL). Stir the mixture for 10 min, and then separate the phases. Extract the aqueous phase with toluene (100 mL), and combine the organic phases. Wash the rich organic with 5% NaCl (100 mL). Transfer the rich organic (total volume ∼600 mL) to a calibrated 2 L, three-neck flask equipped with a mechanical stirrer, thermocouple probe, and concentrator condenser. Concentrate

(18) Alternatively, the dicarboxylic acid can be added as a slurry in a portion of the CH_2Cl_2.

(19) If the reaction stalls, fresh charges of Vilsmeier reagent can be made.

(20) HPLC indicates that all of **3** is consumed within 4 h. The dichloride formation is complete when intermediate peaks at retention times 15.3 and 15.8 min are <0.1 area % each. The retention time for **4** is 21.5 min.

(21) Subsurface addition greatly reduces the amount of airborne TEA·HCl and fogging in the pot. This was accomplished by attaching a piece of Teflon tubing to the tip of the addition funnel.

(22) The reaction is deemed complete when HPLC analysis gives **4** at ≥94 area %. LCMS (ESI) m/z (%): 373.8 (MH^+, 100), 375 (MH + 2, 37%), 377 (MH + 4, 17%). Note that the LCMS used was calibrated at 1 Da off.

(23) The amounts of tetra-*n*-butylammonium hydroxide and KI are based on the input of **3**.

(24) wt % Tetra-*n*-butylammonium hydroxide tends to solidify at <30 °C, and usually requires warming before use to liquify it. A 55 wt % solution is available that reportedly does not solidify at ambient temperatures.

the rich organic to approximately 25% of the starting volume (150 mL) at 40−50 °C under reduced pressure (15−20 inHg vacuum). Add toluene (50 mL) at 40−50 °C. Gradually add *n*-heptane (300 mL, 1.5: 1 ratio with pot volume) at 40−50 °C with good stirring. Heat the resulting slurry to 75 to 80 °C to afford a clear solution, and hold at this temperature range for 10 min.[25] Allow the solution to cool to 20−25 °C (**5** begins to precipitate at <60 °C). When the internal temperature reaches 20−25 °C, cool to 0−5 °C, and stir for 1 h. Filter the slurry cold under vacuum, rinsing the flask with mother liquor as needed. Wash the filter cake with *n*-heptane (100 mL). The product was deliquored and then dried at 45−50 °C under 25−30 inHg vacuum for 8 h (or until the loss on drying is <1%) to give 14.4 g (81 M%) of **5** as fine, colorless rods. mp = 151−154 °C; $[\alpha]^{20}_D$ = −110° (*c* 0.70, CH_2Cl_2);[14] ^{1}H NMR ($CDCl_3$) δ: 8.21 (d, J = 7.66 Hz, 2H), 7.86 (t, J = 7.89, 15.57 Hz, 1H), 4.53 (q, J = 8.15, 9.47, 17.63 Hz, 2H), 4.17 (m, 4H), 1.87 (m, 2H), 1, 05 (d, J = 6.68 Hz, 6H), 0.94 (d, J = 6.71 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 161.84, 146.56, 140.19, 136.82, 125.38, 72.55, 70.61, 32.50; IR (KBr): 1643 cm^{-1}. Anal. Calcd 67.75% C, 7.69% H, 13.94% N for $C_{17}H_{23}N_3O_2$. Found: 67.76% C, 7.66% H, 13.90% N.

***trans*-Dichlororuthenium ((*S,S*)-2,6-Bis(4-isopropyl-2-oxazolin-2-yl)pyridine)(ethylene) (RuPybox-ip), 1.** Equip a 1 L, three-neck flask with a mechanical stirrer, thermocouple probe, condenser, and N_2 inlet/outlet connected to a mineral oil bubbler. A bath for cooling is placed under the flask. Charge ligand **5** (50.0 g, 165.8 mmol) and dichloro(*p*-cymene)ruthenium-(II) dimer (49.1 g, 80.17 mmol) to the flask. Flush the flask with N_2 or argon for at least 15 min. Charge in HPLC grade CH_2Cl_2 (550 mL), and stir the mixture for 5−10 min to afford a solution (a 5 °C exotherm is observed). Bubble ethylene gas through the solution at a moderate rate until the reaction is complete.[17] The addition of ethylene is exothermic, and the temperature should be maintained at 20 ± 10 °C. Upon completion, displace the ethylene gas with N_2 or argon, and filter the solution through Whatman 4 paper. Equip a 10 L, three-neck flask with a mechanical stirrer, thermocouple probe, and N_2 inlet. Charge the flask with *n*-heptane (5.5 L). Add the reaction mixture to *n*-heptane over 30 min with good stirring to allow for rapid dispersion of the solution into the *n*-heptane. After the addition is complete, stir the slurry for 1 h. Filter the slurry on Whatman 4 paper under vacuum, using portions of the mother liquor to rinse out the crystallizing flask as needed. Wash the filter cake with with *n*-heptane (600 mL), and deliquor. Dry the product at 35 to 45 °C under 25−30 inHg vacuum to give **1** in a yield of 69.4 g (83.4 M%). The yield is corrected for 4.9% leftover **5**. mp = 210−225 °C; ^{1}H NMR ($CDCl_3$) δ: 7.89 (s, 3H, pyridine protons), 5.25 (m, 2H, ethylene), 4.78−4.97 (m, 2H, 2 x O*C*H_2 and ethylene), 4.43 (m, 2H, N*CH*), 2.48 (m, 2H, isopropyl methines), 1.00 (d, J = 7.2 Hz, 6H, isopropyl methyls), 0.78 (d, J = 7.2 Hz, 6H, isopropyl methyls); ^{13}C NMR ($CDCl_3$) δ: 163.70, 145.90, 133.46, 123.30, 71.70, 70.90, 70.50, 19.10, 14.30; IR (KBr): 2960, 1598, 1501, 1403, 1388, 1342, 1250, 968 cm^{-1}.

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Supporting Information Available: Spectroscopic data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) **5** is stable in toluene at 100 °C for up to 48 h.