COUPLING OF CONSECUTIVE PYRIDINE RING UNITS FOR OLIGOPYRIDINE SYNTHESIS

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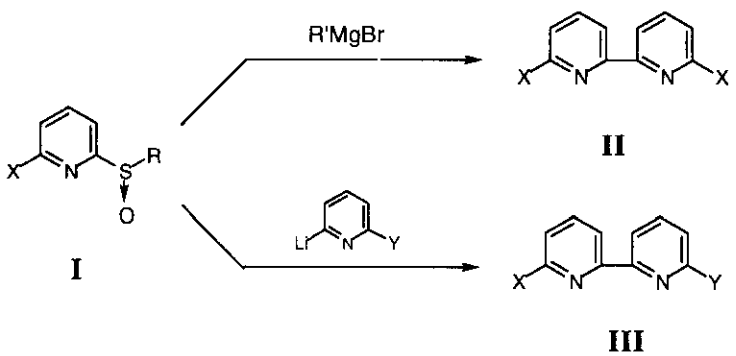
Abstract - The reaction of 2-ethylsulfinyl-6-(ethylthio)pyridine (**2**), 6-ethylsulfinyl-6'-ethylthio-2,2'-bipyridine (**6**), and 6-ethylsulfinyl-6"'-ethylthio-2,2':6',2":6",2'"-quaterpyridine (**10**) with methylmagnesium bromide gave symmetric oligopyridines 6,6'-bis(ethylthio)-2,2'-bipyridine (**4**), 6,6"'-bis(ethylthio)-2,2':6',2":6",2'"-quaterpyridine (**8**), and 6,6""'-bis(ethylthio)-2,2':6',2":6",2'":6'",2"":6"",2"":6"",2"":6"",2"":6"",2""'-octipyridine (**12**) in respective yields of 70, 56, and 3%. On the other hand, the reaction of **6** and **10** with 2-(6-bromopyridinyl)lithium and 6-(2,2'-bipyridinyl)lithium gave the corresponding unsymmetric oligopyridines (**15**, **16**, **13**, and **19**). The reaction with chiral (*S*)-2-{6-[1-(*tert*-butyldimethylsiloxy)-ethyl]pyridinyl}lithium gave optically active oligopyridines (**17**) and (**18**) in 78 and 58% yields, respectively.

INTRODUCTION

Oligopyridines comprised of consecutive pyridine-pyridine rings connected at each 2,6-position have been reported.[1] They have been expected to be not only useful ligands, but also new functional materials.[2] Such expectations are based on their unique characteristics. Oligopyridines including chiral bipyridines are attractive for molecular recognition chemistries[3] as well as asymmetric catalysis.[4] However, the synthesis of oligopyridine is not easy. In particular, the synthesis of chiral oligopyridines has not been reported except some simple chiral bipyridines.[5] Potts recently raised the maximum number of consecutive pyridine rings in oligopyridine synthesis to 10.[6] He prepared internal pyridine rings from the corresponding acyclic precursors by Krohnke's method,[7] but this process was rather tedious steps. Therefore, a general, convenient, and flexible synthetic method for oligopyridine synthesis is needed. In this paper, we report the synthesis of symmetrical and unsymmetrical oligopyridines including chiral oligopyridines by direct pyridine-pyridine ring coupling reactions using (alkylsulfinyl)pyridines with methylmagnesium bromide and pyridinyllithium reagents.

Several methods have been reported for the synthesis of 2,2'-bipyridine.[8] Among them, Krohnke's method is the most popular and reliable so far, but it requires long steps and is limited to the synthesis of simple oligopyridines. Multifunctional oligopyridines, including optically active oligopyridines, have never been synthesized by this method. On the other hand, the direct coupling reaction of pyridine-pyridine rings is straightforward, and much more flexible for the synthesis of a variety of bipyridines, terpyridines, and high-order oligopyridines. In fact, the metal-catalyzed coupling of 2-halopyridines,[9] and the alkyl Grignard-promoted reaction of 2-(alkylsulfinyl)pyridine[10] are useful for obtaining symmetrical bipyridines, but can not be used to obtain unsymmetric bipyridines. We have reported pyridine-pyridine ring coupling using 2-(alkylsulfinyl)pyridines for the synthesis of 2,2'-bipyridines, terpyridines,[11] and some chiral oligopyridines.[12] The key steps are shown in Scheme 1. The coupling reaction of 2-(alkylsulfinyl)pyridines (**I**) with an alkyl Grignard reagent gave symmetrical 2,2'-bipyridine (**II**), while that with 2-pyridinyllithium gave unsymmetrical 2,2'-bipyridine (**III**). If the substituent **X** is an ethylthio group, the coupling products (**II** and **III**) can be transformed to the corresponding ethylsulfinyl derivatives by an appropriate oxidation reaction. The ethylsulfinyloligopyridine derivatives can be subjected to coupling reactions to provide higher-order oligopyridines. Repetition of this process may enable the straightforward synthesis of bis(ethylthio)-oligopyridines.

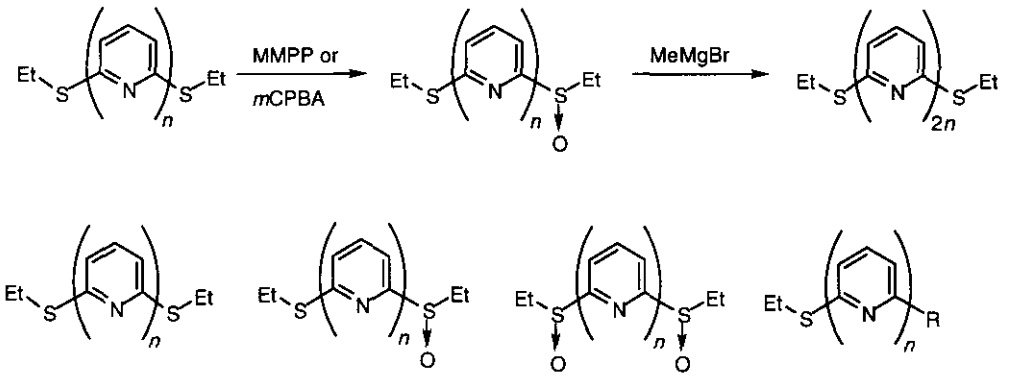


Scheme 1

RESULTS AND DISCUSSION

The synthesis of a symmetrical oligopyridine began with 2,6-bis(ethylthio)pyridine (**1**), which was prepared in 96% yield from 2,6-dichloropyridine and sodium ethylmercaptide in a mixture of DMF and HMPA (4:1). The oxidation of **1** with MMPP (magnesium salt of monoperoxyphthalic acid) gave 2-ethylsulfinyl-6-(ethylthio)pyridine (**2**) in 73% yield along with disulfoxide (**3**) in 16% yield. The sulfoxide (**2**) was treated with methylmagnesium bromide in THF at room temperature to give 6,6'-bis(ethylthio)-2,2'-bipyridine (**4**) in 70% yield. 2-(Ethylthio)pyridine[13] was formed as a by-product due to the unreacted pyridinylmagnesium bromide intermediate, the mechanism for which is discussed later. Bis(ethylthio)bipyridine (**4**) was subjected to the same procedures; *i.e.*, oxidation of the ethylthio group and treatment of the resulting (ethylsulfinyl)bipyridine with methylmagnesium bromide. Oxidation of **4** with MMPP gave monosulfinylbipyridine (**6**) in 54% yield along with disulfinylbipyridine (**7**) in 21% yield. The

reaction of **6** with methylmagnesium bromide in THF gave quaterpyridine (**8**) in 56% yield. 6-Ethylthio-2,2'-bipyridine (**9**) was formed in 11% yield as a by-product. After the second multiplication of pyridine ring units, the sulfide (**8**) was oxidized again. Due to its poor solubility in methanol and water, the oxidation of **8** was carried out in $CHCl_3$ with *m*CPBA. The reaction of **8** was completed within 5 min at -50°C, and gave the desired sulfoxide (**10**) in 47% yield along with disulfoxide (**11**) in 16% yield. However, the third coupling for the synthesis of octipyridine (**12**) was troublesome, due to a formation of an insoluble complex when Grignard reagent was added to a THF solution of **8**. Octipyridine (**12**) was obtained in less than 5% yield. The major product was 6-(ethylthio)quaterpyridine (**13**) in 10% yield, and 34% of the starting material was recovered. The addition of TMEDA improved the solvation of the insoluble magnesium complexes produced from the substrate or products. Nonetheless, the yield did not improve much. Interestingly, a trace amount of methylquaterpyridine (**14**) was unexpectedly formed in 3 % yield. Since this result was reproducible, the substitution reaction of the ethylsulfinyl group with a methyl group surely took place.



1 $n=1$ **2** $n=1$ **3** $n=1$ **5** $n=1$; R = H
4 $n=2$ **6** $n=2$ **7** $n=2$ **9** $n=2$; R = H
8 $n=4$ **10** $n=4$ **11** $n=4$ **13** $n=4$; R = H
12 $n=8$ **14** $n=4$; R = Me

Scheme 2

The ligand coupling reaction has been well documented[14] and the mechanism is shown in Figure 1. First, methylmagnesium bromide attacks the sulfur center of (ethylsulfinyl)pyridine to form the hypervalent intermediate (**A**), from which ethyl methyl sulfoxide and pyridylmagnesium bromide are produced. It can be reacted with the starting (ethylsulfinyl)pyridine to form hypervalent intermediate (**B**). Subsequent pyridine-pyridine coupling gives the high-order oligopyridine eventually. The rate-determining step may be the coupling step. The coupling to give bipyridine ($2n$=2) and quaterpyridine ($2n$=4) proceeded quite smoothly. The terminal pyridines (**5**) and (**9**), which were produced from unreacted pyridinylmagnesium intermediate or hypervalent intermediate (**B**), were the major by-products of the reactions. On the other hand, the reaction of **10** (n=4) was rather messy, and a considerable amount of precipitate was formed, with the

terminal pyridine (**13**) obtained as the major product. Magnesium in the σ-sulfurane intermediate (**B**) was probably stabilized by the strong intramolecular coordination with oligopyridines to produce insoluble materials. This formation may decrease the reactivity on the hypervalent sulfur center to give very little of the desired coupling product (**12**) in the case of high-order oligopyridines.

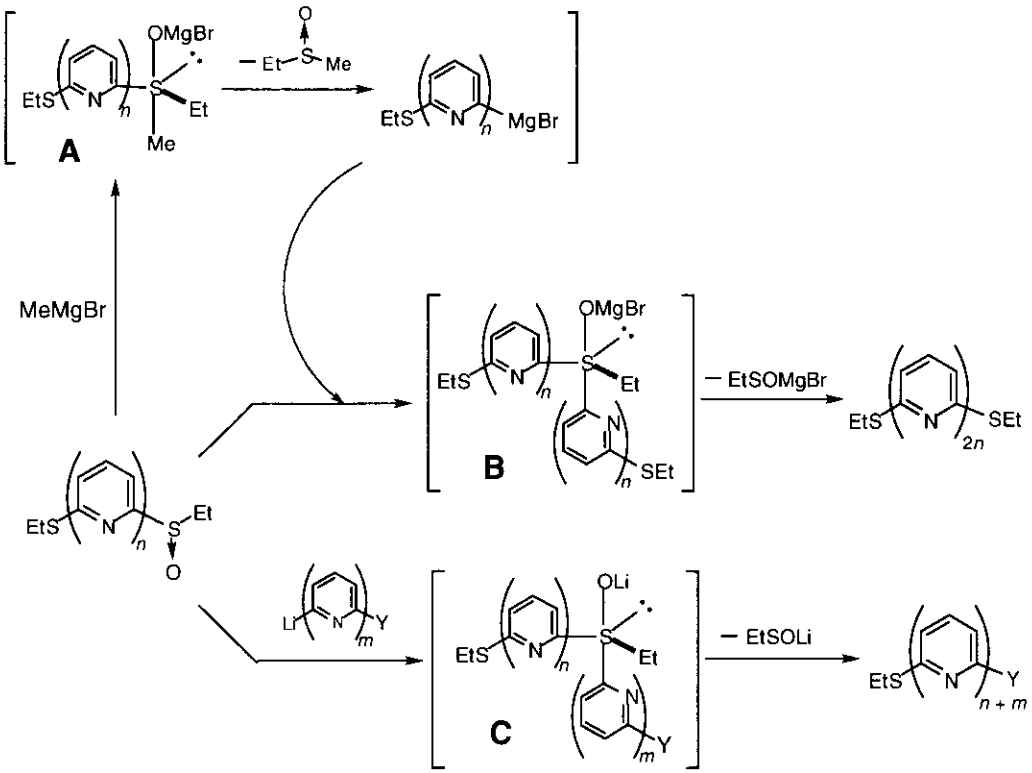
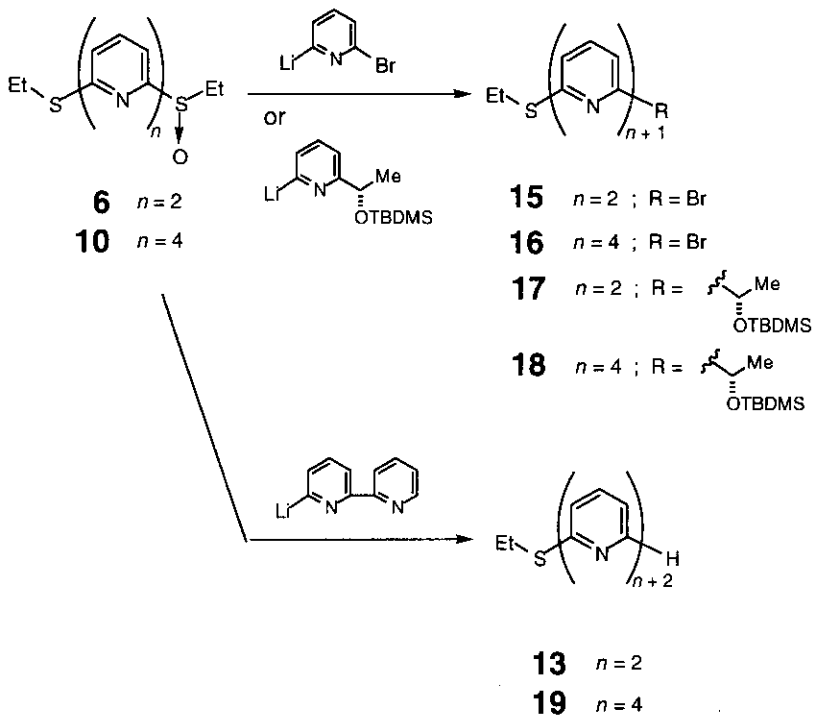


Figure 1

Next, we were interested in the synthesis of unsymmetrical oligopyridines. The basic reaction for the synthesis of unsymmetrical 2,2'-bipyridines has been reported previously.[11] Thus, as shown in Scheme 1, when 2-(alkylsulfinyl)pyridine (**I**) was reacted with 2-pyridinyllithium, 2,2'-bipyridine (**III**) was formed in medium to excellent yield. If this reaction is applied to 6-(ethylsulfinyl)bipyridine (**6**) or 6-(ethylsulfinyl)quaterpyridine (**10**), high-order oligopyridines could be prepared. In fact, when **6** was treated with 2-(6-bromopyridinyl)lithium at -78°C in a mixture of hexane, ether, and THF (1:2:1), 6-bromo-6"-ethylthio-2,2':6',2"-terpyridine (**15**) was obtained in 92% yield. Under the same conditions, the reaction of **10** with 2-(6-bromopyridinyl)lithium gave quinqepyridine (**16**) in 51% yield. Compound (**6**) reacted with 2-pyridinyllithiun with a chiral siloxyethyl group at the 6-position, which was generated from (*S*)-2-bromo-6-[1-(*tert*-butyldimethylsiloxy)ethyl]pyridine[12] and butyllithium, to give optically pure terpyridine (**17**) in 78% yield. Optically active quinqepyridine (**18**) was obtained in 58% yield by the reaction of **10** the same optically active pyridyllithium. In the same manner, **6** was reacted with 6-(2,2'-bipyridinyl)lithium to give quaterpyridine (**13**) in 77% yield. The reaction of **10** with bipyridinyllithium gave sexipyridine (**19**) in 51% yield. The formation of these unsymmetrical oligopyridines can be explained by a ligand coupling reaction *via* the same σ-sulfurane intermediate (**C**), as shown in Figure 1.



Scheme 3

In conclusion, this multiplication reaction of pyridine ring units connected at each 2,6-position on the ring may be quite useful for the synthesis of symmetrical oligopyridines, at least for the four consecutive pyridine rings, and for the synthesis of unsymmetrical oligopyridines, particularly those with a chiral center.

EXPERIMENTAL

General. Melting points were determined on a Yanagimoto Micro Melting Point Apparatus and were uncorrected. ^{1}H and ^{13}C NMR were taken in $CDCl_3$ for ^{1}H (500, 400, or 300 MHz) and for ^{13}C (125, 100, or 75 MHz) using a Jeol LA500D, Jeol GXS 400, Jeol LA300D, or Varian Gemini-300 spectrometer. The chemical shifts were given as δ value relative to internal tetramethylsilane for ^{1}H NMR (0.00 ppm) and $CDCl_3$ for ^{13}C NMR (77.0 ppm). FT-IR spectra were recorded on a Jasco FT/IR-230 as liquid films on NaCl plates or as tablets. MS spectra were obtained on a Jeol MStation instrument. Optical rotation values ($[\alpha]_D$) were determined in $CHCl_3$ using a Jasco DIP-370 polarimeter. TLC analysis were carried out on Merck $60F_{254}$ precoated silica gel plates. Merck silica gel 60 (70-230 mesh) was used for column chromatography. Recycling preparative HPLC was performed on a Japan Analytical Industry LC-908 using a set of JAIGEL-2H and JAIGEL-1H columns.

2,6-Bis(ethylthio)pyridine (1). To a stirred solution of EtSNa prepared from EtSH (15.1 mL, 202 mmol) and NaH (8.08 g, 60% suspension in mineral oil, 202 mmol) in DMF and HMPA (30 mL, 4:1), was added a solution of 2,6-dichloropyridine (9.97 g, 67.4 mmol) in DMF-HMPA (7.5 mL, 4:1) dropwise at 0 °C. After stirring for an additional 10 h, the reaction mixture was quenched with water, and extracted with with diethylether and hexane (500 mL, 1:1). The organic layer was washed with water and brine, and dried over

$MgSO_4$. Evaporation of the solvent gave crude product, which was distilled to give **1** (12.95 g) in 96% yield. Colorless oil; bp 80-81 °C (0.3 mmHg); R_f = 0.70 (5% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (6H, t, J = 7.4 Hz), 3.18 (4H, q, J = 7.4 Hz), 6.84 (2H, d, J = 7.9 Hz), 7.25 (1H, t, J = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 24.2, 117.3, 135.7, 158.6; MS (EI, 70 eV) *m/z* (rel intensity) 199 (M^+, base), 184 (33), 166 (52), 138 (26), 110 (28). Anal. Calcd for $C_9H_{13}NS_2$; C, 54.22; H, 6.57; N, 7.03. Found; C, 54.24; H, 6.70; N, 7.30.

Preparation of (Ethylsulfinyl)pyridines (2 and 6). To a stirred solution of bis(ethylthio)pyridine (**1** or **4**, 15.0 mmol) in MeOH (25 mL) was added magnesium monoperoxyphthalate hexahydrate (4.67 g, 80% activity, 7.55 mmol) in MeOH (25 mL) at 0 °C by several portions. After stirring for an additional 25 min sat. $Na_2S_2O_3$ (5 mL) was added to the reaction mixture. The solution was condensed under reduced pressure, and poured into water and extracted with $CHCl_3$. Organic layer was washed with water and brine, and dried over $MgSO_4$. After removal of the solvent the crude product was chromatographed on a silica gel column (50% EtOAc in hexane to 20% MeOH in EtOAc) to give the desired monosulfinylpyridine majourly along with disulfinylpyridine.

Oxidation of 1; 2-Ethylsulfinyl-6-ethylthiopyridine (2). Yield 73%. Colorless oil; bp 147-148 °C (3 mmHg); R_f = 0.48 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, t, J = 7.4 Hz), 1.36 (3H, t, J = 7.1 Hz), 2.93 (1H, dq, J = 13.5, 7.4 Hz), 3.17 (1H, dq, J = 13.5, 7.4 Hz), 3.20 (2H, q, J = 7.1 Hz), 7.18 (1H, d, J = 7.3 Hz), 7.62 (1H, d, J = 7.3 Hz), 7.67 (1H, t, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.22, 14.3, 24.3, 46.9, 115.6, 122.8, 136.9, 160 3, 163.5; IR (film) 1056 cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 215 (M^+, 14), 199 (94), 198 (41), 184 (31), 183 (30), 166 (42), 138 (27), 110 (49), 69 (28), 61 (base). Anal. Calcd for $C_9H_{13}NOS_2$; C, 50.20; H, 6.08; N, 6.50. Found; C, 50.07; H, 6.21; N, 6.47. **2,6-Bis(ethylsulfinyl)pyridine (3).** Yield 16%. A mixture of diastereomers (1:1). Colorless prisms; mp 56-58 °C (MeOH); R_f = 0.58 (20% MeOH in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (6H, t, J = 7.3 Hz) and 1.23 (6H, t, J = 7.4 Hz), 2.93 (2H, dq, J = 14.9, 7.3 Hz) and 2.94 (2H, dq, J = 14.9, 7.4 Hz), 3.12-3.26 (4H, m), 8.05 (4H, d, J = 7.5 Hz), 8.20 (2H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.32 and 5.34, 47.4 and 47.6, 121.1 and 121.3, 139.4 and 139.5, 164.9 and 165.0; IR (KBr) 1049 cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 231 (M^+, 57), 215 (25), 203 (51), 199 (64), 198 (62), 175 (base), 157 (37), 138 (26), 126 (31), 110 (72), 109 (62), 69 (28). Anal. Calcd for $C_9H_{13}NO_2S_2$; C, 46.73; H, 5.66; N, 6.05. Found; C, 46.89; H, 5.67; N, 6.27.

Oxidation of 4; 6-Ethylsulfinyl-6'-ethylthio-2,2'-bipyridine (6). Yield 54%. Colorless prisms; mp 64-66 °C (EtOAc); R_f = 0.46 (60% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.3 Hz), 1.47 (3H, t, J = 7.3 Hz), 3.00 (1H, dq, J = 13.4, 7.3 Hz), 3.25 (1H, dq, J = 13.4, 7.3 Hz), 3.30 (2H, q, J = 7.3 Hz), 7.22 (1H, dd, J = 7.9, 0.8 Hz), 7.61 (1H, t, J = 7.9 Hz), 7.99 (1H, dd, J = 7.7, 1.4 Hz), 8.05 (1H, t, J = 7.7 Hz), 8.06 (1H, dd, J = 7.9, 0.8 Hz), 8.49 (1H, dd, J = 7.7, 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.44, 14.6, 24.4, 47.5, 116.6, 120.1, 121.5, 122.9, 136.8, 138.5, 154.2, 156.1, 159.0, 163.5; IR (KBr) 1053 cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 292 (M^+, 21), 276 (76), 275 (base), 261 (15), 243 (33), 216 (32), 215 (25), 187 (23). Anal. Calcd for $C_{14}H_{16}N_2OS_2$; C, 57.50; H, 5.51; N, 9.58. Found; C, 57.35; H, 5.45; N, 9.56. **6,6'-Bis(ethylsulfinyl)-2,2'-bipyridine (7).** Yield 21%. A mixture of diastereomers (1:1). Colorless leaflets ; mp 126-128 °C (MeOH); R_f = 0.34 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (6H, t, J = 7.3 Hz), 3.01

(2H, dq, J = 14.8, 7.3 Hz), 3.29 (2H, dq, J = 14.8, 7.3 Hz), 8.03-8.11 (4H, m), 8.46 (2H, dd, J = 7.0, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.44 and 5.46, 47.5 and 47.6, 120.9 and 120.9, 121.8, 138.8, 154.8, 164.0 and 164.0; IR (KBr) 1055 cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 308 (M^+, 33), 278 (39), 277 (76), 276 (base), 275 (40), 261 (30), 243 (57), 216 (40), 215 (26), 201 (22), 187 (27), 183 (23), 89 (26), 69 (34). Anal. Calcd for $C_{14}H_{16}N_2O_2S_2$; C, 54.52; H, 5.23; N, 9.08. Found; C, 54.74; H, 5.37; N, 9.33.

***m*-CPBA Oxidation of 8.** To a stirred solution of **8** (502 mg, 1.17 mmol) in $CHCl_3$ (150 mL) was added a solution of *m*-chloroperbenzoic acid (0.257 g, 80% acticvity, 1.19 mmol) in $CHCl_3$ (25 mL) at –50 °C. After stirring for an additional 5 min, the mixture was quenched with sat. $Na_2S_2O_3$ (5 mL) at –50 °C, and allowed to warm up to rt. The organic layer was washed with sat. $NaHCO_3$, water, and brine, and dried over $MgSO_4$. After removal of the solvent, the crude material was chromatographed on a silica gel column (5% EtOAc in $CHCl_3$ to 5% MeOH in $CHCl_3$) to give **10** in 47% yield (246m g) and **11** in 16% yield (87 mg). **6-Ethylsulfinyl-6'''-ethylthio-2,2':6'2'':6'',2'''-quaterpyridine (10).** Colorless powder; mp 160-162 °C ($CHCl_3$); R_f = 0.37 (50% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7.4 Hz), 1.49 (3H, t, J = 7.4 Hz), 3.05 (1H, dq, J = 13.6, 7.4 Hz), 3.28 (1H, dq, J = 13.6, 7.4 Hz), 3.33 (2H, q, J = 7.4 Hz), 7.22 (1H, dd, J = 7.9, 0.7 Hz), 7.67 (1H, t, J = 7.8 Hz), 8.00 (2H, t, J = 7.8 Hz), 8.03 (1H, dd, J = 7.7, 1.0 Hz), 8.11 (1H, t, J = 7.8 Hz), 8.34 (1H, dd, J = 7.6, 0.7 Hz), 8.42 (1H, dd, J = 7.7, 0.9 Hz), 8.51 (1H, dd, J = 7.8, 1.0 Hz), 8.63 (1H, dd, J = 7.8, 0.9 Hz), 8.70 (1H, dd, J = 7.8, 0.9 Hz), 8.72 (1H, dd, J = 7.8, 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.49, 14.7, 24.5, 47.5, 116.4, 120.2, 121.0, 121.1, 121.2, 121.7, 121.8, 122.4, 136.7, 137.8, 137.9, 138.6, 153.9, 155.0, 155.3, 155.6, 155.7, 156.4, 158.5, 163.6 ; IR (KBr) 1053 cm^{-1}; MS (FAB) *m/z* 447 (M^++H). Anal. Calcd for $C_{24}H_{22}N_4OS_2$; C, 64.55; H, 4.97; N, 12.55. Found; C, 64.64; H, 4.96; N, 12.58. **6,6'''-Bis(ethylsulfinyl)-2,2':6',2'':6'',2'''-quaterpyridine (11).** A mixture of diastereomers (1:1). Colorless powder; mp 197-198 °C ($CHCl_3$); R_f = 0.60 (20% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (6H, t, J = 7.3 Hz), 3.04 (2H, dd, J = 12.8, 7.3 Hz), 3.26 (2H, dd, J = 12.8, 7.3 Hz), 8.00-8.15 (7H, m), 8.45 (2H, d, J = 7.3 Hz), 8.69-8.76 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.49 and 5.49, 47.5 and 47.5, 120.3, 121.4, 121.7 and 121.8, 138.0, 138.6, 138.8, 154.0, 155.3, 156.2, 163.7; IR (KBr) 1046 cm^{-1}; MS (FAB) *m/z* 463 (M^++H). Anal. Calcd for $C_{24}H_{22}N_4O_2S_2$; C, 62.32; H, 4.79; N, 12.11. Found; C, 62.34; H, 4.80; N, 12.27.

Coupling Reaction of (Ethylsulfinyl)pyridines (2 and 6). *To a stirred solution of (ethylsulfinyl)pyridine* (**2** or **6**, 1.4 mmol) in THF (4 mL) was added MeMgBr (1.9 mL, 0.90 *M* in THF, 1.7 mmol) slowly at rt. After stirring for 15 min, the resulting mixture was poured into water and extracted with $CHCl_3$. Organic layer was washed with water and brine and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on a silica gel column to give **4** or **8**. Eluents for the column chromatography are described behind the chemical yield.

Coupling of 2; 6,6'-Bis(ethylthio)-2,2'-bipyridine (4); Yield 70%, 5% EtOAc in hexane. Colorless prisms; mp 83-84 °C (EtOAc); R_f = 0.57 (5% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (6H, t, J = 7.3 Hz), 3.29 (4H, q, J = 7.3 Hz), 7.59 (2H, d, J = 7.8 Hz), 7.60 (2H, t, J = 7.8 Hz), 8.12 (2H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 24.4, 116.3, 122.3, 136.7, 155.5, 158.3; MS (EI, 70 eV) *m/z* (rel intensity) 276 (M^+, base), 261 (23), 243 (51), 216 (36), 215 (17), 187 (15), 183 (11). Anal. Calcd for $C_{14}H_{16}N_2S_2$; C,

60.83; H, 5.83; N, 10.13. Found; C, 60.88; H, 5.82; N, 10.22. **2-(Ethylthio)pyridine (5).**[12] Yield 22%, 5% EtOAc in hexane. R_f = 0.56 (10% EtOAc in hexane); Colorless oil.

Coupling of 6; 6,6'''-Bis(ethylthio)-2,2':6',2'':6'',2'''-quaterpyridine (8). Yield 56%, 5% EtOAc in hexane. Colorless scales; mp 207-209 °C ($CHCl_3$); R_f = 0.37 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (6H, t, *J* = 7.3 Hz), 3.33 (4H, q, *J* = 7.3 Hz), 7.21 (2H, dd, *J* = 7.9, 0.7 Hz), 7.67 (2H, t, *J* = 7.7 Hz), 7.98 (2H, t, *J* = 7.7 Hz), 8.35 (2H, dd, *J* = 7.7, 0.7 Hz), 8.49 (2H, dd, *J* = 7.7, 1.0 Hz), 8.65 (2H, dd, *J* = 7.9, 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 24.5, 116.5, 120.9, 121.0, 122.3, 136.7, 137.7, 155.2, 155.3, 155.7, 158.4; MS (EI, 70 eV) *m/z* (rel intensity) 430 (M^+, base), 415 (13), 401 (44), 397 (41), 366 (52), 342 (46), 341 (33), 310 (23), 309 (24). Anal. Calcd for $C_{24}H_{22}N_4S_2$; C, 66.94; H, 5.15; N, 13.01. Found; C, 67.13; H, 5.11; N, 13.12. **6-Ethylthio-2,2'-bipyridine (9).** Yield 11%, 5% EtOAc in hexane. Colorless oil; R_f = 0.38 (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (3H, t, *J* = 7.3 Hz), 3.30 (2H, q, *J* = 7.3 Hz), 7.18 (1H, dd, *J* = 7.9, 0.9 Hz), 7.29 (1H, ddd, *J* = 7.5, 4.8, 1.1 Hz), 7.61 (1H, t, *J* = 7.8 Hz), 7.81 (1H, td, *J* = 7.8, 2.0 Hz), 8.11 (1H, dd, *J* = 7.7, 0.9 Hz), 8.43 (1H, dd, *J* = 7.9, 2.0 Hz), 8.66 (1H, ddd, *J* = 4.8, 1.7, 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 24.4, 116.3, 121.0, 122.2, 123.7, 136.8, 136.8, 149.0, 155.6, 156.0, 158.4; MS (EI, 70 eV) *m/z* (rel intensity) 216 (M^+, base), 201 (35), 183 (70), 156 (59), 155 (55), 130 (16), 78 (24). Anal. Calcd for $C_{12}H_{11}N_2S$; C, 66.94; H, 5.15; N, 13.01. Found; C, 66.69; H, 5.42; N, 12.89.

Coupling of 10. To a stirred solution of **10** (38 mg, 0.085 mmol) in THF (5 mL) was added MeMgBr (0.35 mL in 0.93 M THF solution, 0.33 mmol) slowly at rt, and the reaction mixture was stirred for 40 min. Then, the resulting green suspension was quenched with water (4 mL) and NaOH (7 mL, in 1M solution). The mixture was extracted with $CHCl_3$ (20 mL X 4), and the combined extracts were were washed with water and brine, and dried over $MgSO_4$. After removal of the solvent, the crude product was passed through a short silica gel column. Elutions with 5% EtOAc in $CHCl_3$ was concentrated and the residual oil was purified by recycle GPC separation to give **12** in 3% yield. Elutions with 7% EtOAc in $CHCl_3$ gave 34% recovery of **10.** Elutions with 10% EtOAc in $CHCl_3$ gave polar materials (25 mg) containing **13** and **14**, which were isolated in 10% and 3% yields respectively, after the purification by recycle GPC separation. **6,6''''''-Bis(ethylthio)-2,2':6',2'':6'',2''':6''',2'''':6'''',2''''':6''''',2'''''':6''''''-octipyridine (12).** Yield 3%. Colorless crystals; mp 220-222 °C ($CHCl_3$); R_f = 0.81 (5% EtOAc in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (6H, t, *J* = 7.4 Hz), 3.33 (4H, q, *J* = 7.4 Hz), 7.22 (2H, dd, *J* = 8.0, 0.8 Hz), 7.67 (2H, t, *J* = 7.8 Hz), 7.73 (2H, d, *J* = 7.6 Hz), 7.81 (2H, t, *J* = 7.9 Hz), 7.94 (2H, t, *J* = 7.6 Hz), 7.98 (2H, t, *J* = 7.8 Hz), 8.34 (2H, dd, *J* = 7.8, 0.6 Hz), 8.46 (2H, dd, *J* = 7.8, 0.8 Hz), 8.49 (2H, dd, *J* = 7.6, 0.6 Hz), 8.50 (2H, dd, *J* = 7.9, 1.5 Hz), 8.64 (4H, td, *J* = 7.9, 0.9 Hz); MS (FAB) *m/z* 739 (M^++H); HRMS Calcd for $C_{44}H_{35}N_8S_2$, 739.2426; Found *m/z* 739.2402. **6-Ethylthio-2,2':6',2'':6'',2'''-quaterpyridine (13).** Colorless crystals; mp 157-158 °C (EtOAc); R_f = 0.60 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (3H, t, *J* = 7.3 Hz), 3.33 (2H, q, *J* = 7.3 Hz), 7.21 (1H, dd, *J* = 7.9, 0.7 Hz), 7.35 (1H, ddd, *J* = 7.4, 4.8, 1.2 Hz), 7.67 (1H, t, *J* = 7.8 Hz), 7.88 (1H, td, *J* = 7.7, 1.7 Hz), 7.99 (1H, t, *J* = 7.8 Hz), 8.00 (1H, t, *J* = 7.8 Hz), 8.35 (1H, d, *J* = 7.7 Hz), 8.49 (1H, td, *J* = 7.2, 0.9 Hz), 8.66 (3H, dd, *J* = 7.9, 0.9 Hz), 8.72 (1H, dd, *J* = 7.9, 0.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 24.5, 116.5, 120.9, 121.0, 121.0, 121.1(2C), 122.3, 123.8, 136.7, 136.9, 137.7, 137.8, 149.1, 155.2, 155.3(2C), 155.4, 155.7, 156.3, 158.4; MS (EI, 70 EV) *m/z* (rel intensity) 370 (M^+, base), 355 (20), 337 (49), 310 (54), 309 (51), 155 (15). Anal. Calcd for $C_{22}H_{18}N_4S$; C, 71.32; H, 4.90; N, 15.12. Found;

C, 71.40; H, 4.95; N, 12.89. **6-Ethylthio-6'''-methyl-2,2':6',2'':6'',2'''-quaterpyridine (14).** Colorless crystals; mp 190-192 °C ($CHCl_3$); R_f = 0.34 (10% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (3H, t, *J* = 7.4 Hz), 2.60 (3H, s), 3.27 (2H, q, *J* = 7.4 Hz), 7.14 (1H, d, *J* = 7.3 Hz), 7.15 (1H, dd, *J* = 7.9, 1.7 Hz), 7.60 (1H, t, *J* = 7.8 Hz), 7.69 (1H, t, *J* = 7.7 Hz), 7.91 (2H, t, *J* = 7.8 Hz), 8.29 (1H, dd, *J* = 7.7, 0.8 Hz), 8.37 (1H, d, *J* = 7.8 Hz), 8.43 (2H, ddd, *J* = 7.8, 1.7, 1.1 Hz), 8.57 (1H, dd, *J* = 7.8, 0.9 Hz), 8.60 (1H, dd, *J* = 7.8, 1.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 24.5, 24.7, 116.5, 118.2, 120.9(2C), 121.1(2C), 122.3, 123.3, 136.7, 137.0, 137.7(2C), 155.1, 155.3, 155.4, 155.6, 155.7(2C), 157.9, 158.4; MS (EI, 70 eV) *m/z* (rel intensity) 384 (M^+, base), 369 (22), 351 (52), 324 (77), 323 (41), 256 (29), 149 (47); HRMS Calcd for $C_{23}H_{20}N_4S$ M^+, 384.1409; Found *m/z* 384.1395.

Coupling of Sulfinylpyridines (6 and 10) with Pyridinyllithiums . To a stirred solution of bromopyridine (2.2 mmol) in a mixture of hexane, diethyl ether, and THF (20 mL, 1:2:1) was added *n*-BuLi in THF (1.5 mL, 1.56 M, 2.34 mmol) slowly at –78 °C. To the resulting solution of pyridinyllithium was added a solution of sulfoxide (1.4 mmol) in THF (5 mL) slowly at –78 °C. After stirring for an additional 10 min, the mixture was poured into water and extracted with $CHCl_3$. The organic layer was washed with water and brine and dried over $MgSO_4$. After removal of the solvent the residue was chromatographed on a silica gel column. Eluents for the column chromatography are indicated behind the chemical yield.

6-Bromo-6''-ethylthio-2,2':6',2''-terpyridine (15). Yield 92%, 10% EtOAc in hexane. Colorless microneedles; mp 133.5-134 °C (EtOAc); R_f = 0.63 (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (3H, t, *J* = 7.3 Hz), 3.32 (2H, q, *J* = 7.3 Hz), 7.21 (1H, dd, *J* = 8.0, 0.6 Hz), 7.51 (1H, dd, *J* = 7.9, 0.7 Hz), 7.64 (1H, t, *J* = 7.8 Hz), 7.70 (1H, t, *J* = 7.7 Hz), 7.94 (1H, t, *J* = 7.9 Hz), 8.27 (1H, dd, *J* = 7.7, 0.7 Hz), 8.43 (1H, dd, *J* = 7.8, 0.8 Hz), 8.49 (1H, dd, *J* = 7.9, 0.9 Hz), 8.57 (1H, dd, *J* = 7.7, 0.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 24.5, 116.4, 119.8, 121.4, 121.5, 122.4, 128.0, 136.7, 137.9, 139.1, 141.5, 153.6, 155.3, 155.4, 157.4, 158.5; MS (EI, 70 eV) *m/z* (rel intensity) 373, 371 (M^+, base, 97), 358, 356 (21, 21), 340, 338 (48, 49), 313 (43), 312 (37), 311 (43), 310 (29), 230 (31), 149 (50). Anal. Calcd for $C_{17}H_{14}N_3BrS$; C, 54.85; H, 3.79; N, 11.29. Found; C, 54.65; H, 3.78; N, 11.36.

6-Bromo-6''''-ethylthio-2,2':6',2'':6'',2''':6''',2''''-quinqepyridine (16). Yield 51%, 5% EtOAc in hexane. Colorless powder; mp 289-290 °C ($CHCl_3$); R_f = 0.80 (5% EtOAc in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (3H, t, *J* = 7.2 Hz), 3.32 (2H, q, *J* = 7.2 Hz), 7.20 (1H, dd, *J* = 7.2 Hz), 7.51 (1H, dd, *J* = 7.0 Hz), 7.65 (1H, t, *J* = 7.6 Hz), 7.72 (1H, t, *J* = 7.4 Hz), 7.97-8.03 (3H, m), 8.34 (1H, d, *J* = 7.6 Hz), 8.46 (1H, d, *J* = 7.4 Hz), 8.49 (1H, d, *J* = 7.0 Hz), 8.62 (2H, t. *J* = 8.0 Hz), 8.67 (2H, dm, *J* = 7.0 Hz), 8.70 (1H, d, *J* = 7.6 Hz); MS (FAB) *m/z* 548 (M^++Na). HRMS Calcd for $C_{27}H_{20}N_5BrNaS^+$, 550.0500 and 548.0521; Found 550.0476 and 548.0477.

(*S*)-6-{1-(*tert*-Butyldimethylsiloxy)ethyl}-6''-ethylthio-2,2':6',2''-terpyridine (17). Yield 78%, 7.5% EtOAc in hexane. Colorless powder; mp 75-76 °C (benzene); $[\alpha]_D^{23}$ –21.7° (*c* 2.67, $CHCl_3$); R_f = 0.33 (5% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.12 (3H, s), 0.95 (9H, s), 1.48 (3H, t, *J* = 7.4 Hz), 1.56 (3H, d, *J* = 6.5 Hz), 3.33 (2H, q, *J* = 7.4 Hz), 5.05 (1H, q, *J* = 6.5 Hz), 7.20 (1H, d, *J* = 7.7 Hz), 7.58 (1H, d, *J* = 7.7 Hz), 7.65 (1H, t, *J* = 7.7 Hz), 7.93 (1H, t, *J* = 7.7 Hz), 8.32 (1H, dd, *J* = 7.7, 1.1 Hz), 8.43 (1H, dd, *J* = 7.7, 1.1 Hz), 8.45 (1H, d, *J* = 7.7 Hz), 8.45 (1H, d, *J* = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.9,

–4.7, 14.7, 18.3, 24.5, 25.5, 25.9, 72.2, 116.4, 119.0(2C), 119.3, 120.6, 121.1, 122.2, 125.9, 136.7, 137.3, 137.4, 137.6, 155.1, 158.3, 165.2; MS (EI, 70 eV) *m/z* (rel intensity) 394 (M^+–Bu^t, base). Anal. Calcd for $C_{25}H_{33}N_3OSSi$; C, 66.48; H, 7.36; N, 9.30. Found; C, 66.72; H, 7.14; N, 9.36.

(*S*)-6-{1-(*tert*-Butyldimethylsiloxy)ethyl}-6""-ethylthio-2,2':6',2":6",2"':6"',2"":6""-quinqepyridine (18). Yield 58%, 5% EiOAc in hexane. Colorless powder; mp 249-250 °C (benzene); $[\alpha]_D^{23}$ –19.6° (*c* 0.78, $CHCl_3$); R_f = 0.61 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.13 (3H, s), 0.96 (9H, s), 1.49 (3H, t, *J* = 7.3 Hz), 1.57 (3H, d, *J* = 6.4 Hz), 3.34 (2H, q, *J* = 7.3 Hz), 5.07 (1H, q, *J* = 6.4 Hz), 7.22 (1H, d, *J* = 8.2 Hz), 7.60 (1H, d, *J* = 7.7 Hz), 7.67 (1H, t, *J* = 8.2 Hz), 7.87 (1H, t, *J* = 7.8 Hz), 8.00 (2H, td, *J* = 7.8, 2.9 Hz), 8.03 (1H, dd, *J* = 7.7, 1.1 Hz), 8.37 (1H, d, *J* = 7.7 Hz), 8.48-8.52 (3H, m), 8.67-8.72 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.8, –4.7, 14.7, 18.3, 24.5, 25.5, 25.9, 72.2, 116.5, 119.1, 119.3, 120.8, 120.9, 121.0(2C), 121.1(2C), 122.3, 136.7, 137.4(2C), 137.7, 151.1, 151.2, 154.8, 155.2, 155.3, 155.4, 155.4, 155.7, 155.7, 158.4, 165.3; MS (EI, 70 eV) *m/z* (rel intensity) 605 (M^+, 3), 548 (base). Anal. Calcd for $C_{35}H_{39}N_5OSSi$; C, 69.38; H, 6.49; N, 11.56. Found; C, 69.61; H, 6.58; N, 11.55.

6-Ethylthio-2,2':6',2":6",2"':6"',2"":6"",2""':6""'-sexipyridine (19). Yield 51%, 5% MeOH in $CHCl_3$. Colorless powder; mp >300 °C ($CHCl_3$); R_f = 0.24 (1% MeOH in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (3H, t, *J* = 7.4 Hz), 3.42 (2H, q, *J* = 7.4 Hz), 7.23 (2H, d, *J* = 7.1 Hz), 7.36 (1H, m), 7.68 (1H, t, *J* = 7.7 Hz), 7.90 (1H, td, *J* = 7.8, 1.8 Hz), 8.02 (2H, t, *J* = 7.7 Hz), 8.06 (2H, t, *J* = 7.6 Hz), 8.38 (1H, dd, *J* = 7.7, 0.7 Hz), 8.50 (1H, dd, *J* = 8.0, 0.9 Hz), 8.52 (1H, dd, *J* = 7.6, 0.9 Hz), 8.67-8.75 (8H, m); MS (FAB) *m/z* 547 (M^++Na); HRMS Calcd for $C_{32}H_{24}N_6NaS^+$, 547.1681; Found 547.1683.

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REFERENCES

1. K. T. Potts, M. J. Cipulla, P. Ralli, and G. Theodoridis, *J. Am. Chem. Soc.*, 1981, **103**, 3585; K. A. Gheysen, K. T. Potts, H. C. Hurrell, and H. D. Abruna, *Inorg. Chem.*, 1990, **29**, 1589; E. C. Constable, S. M. Elder, J. Healy, and D. A. Tocher, *J. Chem. Soc., Dalton Trans.*, 1990, 1669.
2. V. Balzani, A. Juris, and M. Venturi, *Chem. Rev.*, 1996, **96**, 759; E. C. Constable, "Metals and Ligand Reactivity", VCH Verlagsgesellschaft, Weinheim, 1996; E, C. Constable, M. D. Ward, and D. A. Tocher, *J. Am. Chem. Soc.*, 1990, **112**, 1256; K. T. Potts, *Bull. Soc. Chim. Belg.*, 1990, **99**, 741.
3. P. Baxter, J. -M. Lehn, A. DeCian, and J. Fisher, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 69; W. Zarges, J. Hall, J. -M. Lehn, and C. Bolm, *Helv. Chim. Acta*, 1991, **74**, 1843; T. W. Bell and H. Jousselin, *Nature*, 1994, **367**, 441; E. C. Constable, *Nature*, 1994, **367**, 415.
4. H. Brunner and W. Zettlmeier, 'Handbook of Enantioselective Catalysis', Vol. II., VCH Verlagsgesellschaft, Weinheim, 1993.
5. S. Gladiali, G. Chelucci, F. Soccolini, G. Delogu, and G. Chessa, *J. Organomet. Chem.*, 1989, **370**, 285; C. Bolm, M. Ewald, M. Felder, and G. Schlingloff, *Chem. Ber.*, 1992, **125**, 1169.

6. K. T. Potts, K. A. G. Raiford, and M. Keshavarz-K, *J. Am. Chem. Soc.*, 1993, **115**, 2793.
7. F. Krohnke, *Synthesis*, 1976, 1.
8. L. A. Summers, 'The Bipyridines' in "*Adv. in Heterocyclic Chem.*", Vol. 35, p. 281, Academic Press, Inc. 1984.
9. P. E. Fanta, *Synthesis*, 1974, 9; E. C. Constable, and R. Chotalia,, *J. Chem. Soc., Chem. Commun.*, 1992, 64.
10. S. Oae, T. Kawai, and N. Furukawa, *Tetrahedron Lett.*, 1984, **25**, 69; S. Oae, T. Kawai, and N. Furukawa, *Tetrahedron Lett.*, 1984, **25**, 2549.
11. J. Uenishi, T. Tanaka, S. Wakabayashi, S. Oae, and H. Tsukube, *Tetrahedron Lett.*, 1990, **31**, 4625; J. Uenishi, T. Tanaka, K. Nishiwaki, S. Wakabayashi, S. Oae, and H. Tsukube, *J. Org. Chem.*, 1993, **58**, 4382.
12. J. Uenishi, K. Nishiwaki, S. Hata, and K. Nakamura, *Tetrahedron Lett.*, 1994, **35**, 7973.
13. N. Furukawa, F. Takahashi, K. Kishimoto, H. Morita, and S. Oae, *Heterocycles*, 1980, **14**, 1273.
14. S. Oae and Y. Uchida, *Acc. Chem. Res.*, 1991, **2**, 202; S. Oae, *Rev. Heteroatom Chem.*, 1992, **4**, 195.

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