New chiral bis(oxazolinyl)bipyridine ligands and application in the iron catalyzed asymmetric hydrosilylation of ketones

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C_2 symmetrical 6,6′-bis(oxazolinyl)-2,2′-bipyridine (*bipybox*) chiral ligands have been synthesized from readily available 2,2′-bipyridine. Catalytic asymmetric hydrosilylation of ketones was studied using this family of ligands in the presence of iron(II) acetate.

Introduction

The reduction of unsaturated compounds containing C=C, C=N and C=O bonds is among the most studied and probably the most diversified reactions. There is a large variety of methods to perform the reduction of double bonds.[1] Our work focuses on the asymmetric reduction of the C=O carbonyl group using the hydrosilylation reaction.[2] There is a large interest to develop procedures affording enantiomerically pure secondary alcohols. Their preparation is essential because they are important building blocks in the synthesis of biologically important products. Especially, chiral secondary alcohols are suitable key intermediates for the synthesis of biologically active components and hence have emerged as important targets in the pharmaceutical industry.[3] Iron is one of the most abundant metals on Earth; it is inexpensive, environmentally benign, and relatively nontoxic in comparison with other metals. From a green chemistry point of view, the development of new Fe-catalyzed methods is of great excitement.[4]

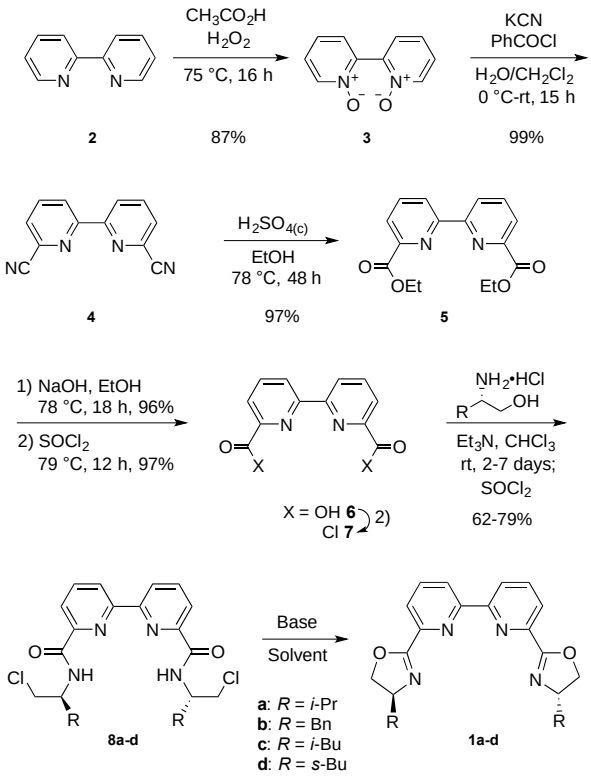
Many catalysts are derived from rare metals, and their price or toxicity prevents their use on an industrial scale. Iron, which is ubiquitous, is thus becoming one of the most versatile transition metals. Various reviews have been published in the field of asymmetric catalysis using iron.[1c,5]

The asymmetric hydrosilylation of ketones was investigated by Nishiyama using $Fe(OAc)_2$ with chiral tridentate bis(oxazoline) ligands, such as pyridine bis(oxazoline) (*pybox-bn*), or bis(oxazolinephenyl)amine (*bopa*) and bis(oxazolinyl)phenyl (*phebox*) ligands.[6] The synthesis and structural characterization of the first chiral iron complexes prepared from

bis(oxazolinyl)phenyl ligands resulting from the oxidative addition of $Fe_2(CO)_9$ to 2-bromo-substituted ligands *phebox* was also disclosed.[7] The corresponding Fe^{II} *phebox* complex was used in the enantioselective hydrosilylation of ketones. The enantioselectivity of the hydrosilylation of ketones was further improved by ligand design.[8] Bulky substituents on the oxazoline ring led to a higher enantioselectivity (up to 88% *ee*). Gade described the synthesis of well-defined iron complexes containing a bidentate ligand and new enantiopure tridentate N–N–N donor ligands, and used the obtained Fe complex in the asymmetric hydrosilylation of ketones.[9] More recently, Gade also developed chiral Fe^{II} alkyl and Fe^{II} alkoxide complexes bearing bis(oxazolinyl-methylidene)isoindoline (*boxmi*) pincers as stereodirecting ligands, which have been employed as catalysts for enantioselective hydrosilylation reactions with unprecedented activity and selectivity.[10] Chirik studied *pybox* and *box* ligands for the hydrosilylation reaction of ketones.[11] Following the same synthetic protocol used for the bis(imino)pyridine Fe^{II} dialkyl derivatives, the corresponding *pybox* and *box* Fe^{II} dialkyl complexes have been also isolated and characterized. Although high conversions were reported for the hydrosilylation of various ketones, the chiral induction of these systems was rather poor (up to 54% *ee*). Togni synthesized novel diamine ligands and used them in association with $Fe(acac)_2$ to promote the asymmetric reduction of acetophenone using phenylsilane.[12] Beller developed a highly enantioselective reduction of ketones by selecting (*S*,*S*)-Meduphos among a series of phosphine ligands.[13] Hunang developed a series of Fe^{II} complexes of chiral iminopyridine-oxazoline (*IPO*) ligands.[14] The most sterically hindered Fe^{II} catalyst exhibits excellent activity (up to 99% yield) and high enantioselectivity (up to 93% *ee*) in the asymmetric hydrosilylation of aryl ketones.

Results and discussion

Three novel 6,6′-bis(oxazolinyl)-2,2′-bipyridine ligands **1b-d** and already known *bipybox-i-Pr* **1a** ligand were prepared from 2,2′-



Scheme 1. Synthesis of *bipybox* ligand

bipyridine **2** via a seven-step synthesis

(Scheme 1).[15] 2,2′-Bipyridine **2** was oxidized to bis-*N*-oxide **3** using hydrogen peroxide in glacial acetic acid. α-Bis-cyanation of bis-*N*-oxide **3** with KCN and benzoyl chloride yielded dinitrile **4** in excellent yield.[15c] Conversion of **4** into the corresponding 6,6′-bis(ethoxycarbonyl)-2,2′-bipyridine **5** was performed by stirring **4** in ethanol and sulfuric acid. After two days, **5** was afforded as a white solid.[15c] **5** was then hydrolyzed in basic conditions to give 6,6′-dicarboxy-2,2′-bipyridine acid **6** in a good yield. The resulting dicarboxylic acid **6** was treated with $SOCl_2$ at reflux to give acid chloride **7** in excellent yield.[15a] Condensation of **7** with 2 equivalents of various amino alcohols followed after two days by the addition of $SOCl_2$ at room temperature afforded the corresponding bis-amidochlorides **8a-d**. The previously described cyclization procedure (NaOH/MeOH)[15a] was employed successfully to prepare *bipybox-i-Pr* **1a** in an excellent yield (Table 1).

Table 1 Conditions for the synthesis of *bipybox* ligands

Entry	R	Base	Solvent		Yield **1** (%)
1[a]	*i*-Pr	NaOH	MeOH	**1a**	92
2[b]	Bn	NaOH	CH_2Cl_2	**1b**	91
3[c]	*i*-Bu	NaH	THF	**1c**	80
4[c]	*s*-Bu	NaH	THF	**1d**	85

Condition: a) **8a**, 6 N NaOH, MeOH, 40 °C, 2 days; b) **8b**, 6 N NaOH, CH_2Cl_2, 40 °C, 7 days; c) **8c**/**8d**, NaH (3.8–4.1 equiv.), THF, rt, 7 days.

Treatment of **8b-d** with NaOH in MeOH was ineffective, and the starting bis-amidochloride **8b-d** was quantitatively recovered. This is probably explained by the low solubility of **8b-d** in methanol. However, *bipybox-Bn* **1b** was obtained by cyclization of corresponding bis-amidochloride **8b** by using 6 N NaOH as a base in CH_2Cl_2 giving an excellent yield after recrystallization. The change in the conditions by using the NaH in THF gave the *bipybox-i-Bu* **1c**, *bipybox-s-Bu* **1d** in a good yield after 7 days at room temperature.

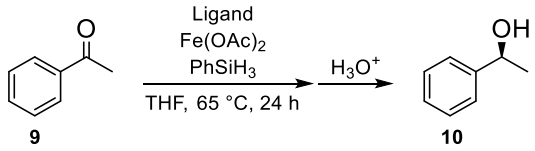
Following our studies in iron catalyzed asymmetric catalysis,[16] we want to disclose our preliminary results using iron(II) acetate conjointly with the aforementioned new series of chiral ligands for the study of the asymmetric hydrosilylation of ketones.

Initially, several chiral *bipybox* ligands were tested for the reduction of acetophenone **9** to 1-phenylethanol **10** by using a given set of conditions. Structurally derived *bipybox* ligands, such as *bipybox-i-Pr* **1a**, *bipybox-Bn* **1b**, *bipybox-i-Bu* **1c**, and *bipybox-s-Bu* **1d**, have been used (Table 2) for the asymmetric hydrosilylation of acetophenone in the presence of $Fe(OAc)_2$ as a catalyst and $PhSiH_3$ as a reducing agent in THF as a solvent to give good to excellent yields of corresponding alcohol **10** (80–90%), but poor enantioselectivities. No reaction was observed using either $FeCl_2$, $FeBr_2$, $Fe(OTf)_2$ or $Fe(ClO_4)_2{\cdot}6H_2O$ as a catalyst. Among the salts tested, $Fe(OAc)_2$ was found to be optimal in terms of conversion.

Using these ligands and $Fe(OAc)_2$, different hydride sources, such as $(EtO)_2MeSiH$, Ph_2SiH_2 and poly(methylhydroxysilane)

(PMHS), were surveyed, but $PhSiH_3$ showed better reactivity and selectivity. We also observed a small temperature effect on the selectivity of catalyst. Typically, when the reaction was carried out at room temperature the conversion was slightly lowered and no enantioselectivity was observed. Various organic solvents such as diethyl ether, dichloromethane, and toluene have been studied but the best results have been obtained using THF as solvent.

Table 2 Ligand screening for the asymmetric hydrosilylation of acetophenone using $Fe(OAc)_2$-ligand.



Entry	Ligand	Yield (%)	*er*
1	bipybox- *i*-Pr **1a**	85	40:60
2	bipybox-Bn **1b**	90	55:45
3	bipybox-*i*-Bu **1c**	85	52:48
4	bipybox-*s*-Bu **1d**	80	52:48

Conditions: $Fe(OAc)_2$ (5 mol %), ligand (6 mol %), acetophenone, $PhSiH_3$ (2 equiv.), THF, 65 °C, 24 h.

The pre-catalyst prepared from $FeCl_2$ (5 mol %) and *bipybox-i-Pr* **1a** (6 mol %) was also tentatively activated using $NaBEt_3H$ (10 mol %).[14] The resulting catalytic system was active for the hydrosilylation of acetophenone **9** using several common silanes. After 24 h, the hydrosilylation product was converted to 1-phenylethanol **10** after acidic work up. Ph_2SiH_2 (2 equiv.) and $PhSiH_3$ (2 equiv.) showed good reactivity, giving 75% and 65% yield, respectively, but no enantioselectivity was observed. We have also checked the effect of $AgBF_4$ (20 mol %) as an additive,[15a] used in the presence of $FeCl_2$ (10 mol %) and *bipybox-i-Pr* **1a** (12 mol %), using Ph_2SiH_2 (2 equiv.) and $PhSiH_3$ (2 equiv.) as silane sources (65 ºC, 24 h), but no conversion was observed and the unreacted product was recovered.

Conclusions

We have presented efficient protocols for the synthesis of three new chiral bis(oxazolinyl)bipyridine ligands starting from 2,2′-bipyridine in seven steps. We have used the newly synthesized ligands, such as *bipybox-i-Bu*, *bipybox-s-Bu*, *bipybox-Bn* and *bipybox-i-Pr*, in the presence of $Fe(OAc)_2$ as a catalyst in the enantioselective hydrosilylation of aceto-phenone using $PhSiH_3$ as reducing agent. The enantioselectivities of the reactions were not yet satisfactory using *bipybox-i-Bu*, *bipybox-s-Bu*, *bipybox-Bn*, but it was demonstrated that a promising enantioselectivity was obtained with *bipybox-i-Pr* ligand used with $Fe(OAc)_2$, together with $PhSiH_3$ as the hydride source, in the hydrosilylation of acetophenone. Our method has the advantage of using a cheap and environmentally benign Lewis acid. The use of these new chiral ligands, complexed *in situ* with various Fe^{II} sources, either under organic or aqueous conditions, is now under investigation for the asymmetric hydrosilylation of various ketones. Further studies to expand the scope and generality of our method are in progress.

Experimental part

General information. All chemicals were commercially available. The *bipybox* ligand **1a** was synthesized according to known procedures.[15] The amino alcohols were prepared from corresponding commercially available amino acids by using already known procedures.[17] Solvents (THF, CH_2Cl_2, Et_2O, $CHCl_3$) were distilled prior to use. Thin-layer chromatography (TLC) was carried out on 250 μm commercial silica gel plates and compounds were visualized using UV absorbance and/or aqueous $KMnO_4$. Flash column chromatography was performed on silica gel (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 400 MHz, Varian Inova 500 MHz spectrometer in $CDCl_3$, D_2O or DMSO-d_6. For ^1H NMR (400 MHz), chemical shift were reported in ppm downfield from tetramethylsilane (TMS) used as internal standard (δ = 0 ppm), and coupling constant and integration (in Hz). For ^{13}C NMR (500 MHz), $CDCl_3$ was used as internal standard (δ = 77.23 ppm) and spectra were obtained with complete proton decoupling. Chiral HPLC was performed using Daicel Chiracel OD-H chiral column, eluting with *n*-hexanes and *i*-propanol. IR spectra were recorded on a NICOLET 380 FT–IR spectrometer with ZnSn ATR accessory and are reported in reciprocal centimeter (cm^{-1}). Melting points (mp) are uncorrected and were recorded on a MEL-TEMP® melting point apparatus.

Reduction of acetophenone. In a glass tube, $Fe(OAc)_2$ (4.4 mg, 0.025 mmol) and *bipybox-i-Pr* (11.4 mg, 0.03 mmol) were added to distilled THF (1 mL). The mixture was stirred for 1 h in a preheated oil bath at 65 ºC under argon. After removal of the oil bath, acetophenone (60.1 mg, 0.5 mmol) and $PhSiH_3$ (120 μL, 1 mmol) were added with a syringe under argon. The mixture was stirred for 20 h at 65 ºC and the reaction was monitored by TLC; hexane: ethyl acetate (9:1). At 0 ºC, aq. HCl (2N, 2 mL) was added to quench the reaction. After stirred for 1 h, the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine and aq. $NaHCO_3$ and dried over $MgSO_4$. After concentration, the residue was purified by silica gel column chromatography to give the desired alcohol as colorless oil (51.9 mg, 0.43 mmol) in a 85% yield and 20% *ee*.

^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.40 ppm (m, 2H); 7.25–7.30 (m, 3H), 4.89–4.92 (m, 1H), 1.49–1.56 (d, ^3J = 6.5 Hz, 3H). HPLC conditions: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 0.8 mL/min, wavelength = 254 nm, t_R = 9.8 min (*S*), t_R = 11.6 min (*R*).

2,2'-Bipyridine-*N*,*N*'-dioxide (3).[15b] A solution of 30% aqueous hydrogen peroxide (68 mL) was added dropwise to 2,2′-bipyridine **2** (15.1 g, 96.0 mmol) in glacial acetic acid (90 mL) at a rate that maintained the temperature between 70 and 80 °C. This mixture was stirred at 75 °C for 15 h. The colorless solution was then cooled to room temperature, and acetone (330 mL) was

added to precipitate the product as a white solid, which was collected by filtration and air-dried (15.8 g, 87% yield). mp: 298 °C (lit. 296–298 °C).[18] ^{1}H NMR (400 MHz, D_2O): δ 8.27–8.32 (m, 2H), 7.68 (dd, ^3J = 8.0, 7.3 Hz, 2H), 7.54–7.62 (m, 4H) ppm. ^{13}C NMR (150 MHz, D_2O): δ 141.68, 139.59, 131.36, 128.77, 128.35 ppm. IR (ZnSn): 3037, 1473, 1426, 1297, 1248 cm^{-1}.

6,6′-Dicyano-2,2′-bipyridine (4). Using a variation of a known procedure,[15c] 2,2′-bipyridine-*N*,*N*′-dioxide **3** (5.0 g, 26.6 mmol) and potassium cyanide (10.4 g, 159.3 mmol) were dissolved in water (53 mL). To this solution cooled at 0 °C, benzoyl chloride (19.2 g, 136.4 mmol) in dichloromethane (27 mL) were added dropwise. The reaction mixture was stirred for 16 h at room temperature. The precipitate was filtered, washed with ethanol and dried at room temperature. The product was obtained as a white solid (5.5 g, 99% yield). mp: 257 °C (lit. 255 °C).[19] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, ^3J = 8.0 Hz, 2H), 8.02 (dd, ^3J = 7.9, 7.9 Hz, 2H), 7.78 (d, ^3J = 7.9 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.51, 138.41, 133.38, 129.09, 124.66, 117.04 ppm. IR (ZnSn): 1695, 1575, 1433, 1156 cm^{-1}.

6,6′-Bis(ethoxycarbonyl)-2,2′-bipyridine (5).[15c] To a solution of 6,6′-dicyano-2,2′-bipyridine **4** (7.2 g, 34.7 mmol) in ethanol (140 mL), concentrated sulfuric acid (63 mL) was added dropwise. The reaction mixture was heated to reflux for 2 days. The solution was then poured over ice (30 g) and stirred for 2 h, then extracted with dichloromethane (3 x). The solution was washed with brine, dried over $MgSO_4$ and evaporated to obtain bis(ethoxy-carbonyl)-2,2′-bipyridine as a white solid (10.0 g, 97% yield). mp: 138 °C (lit. 140–141 °C).[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, ^3J = 8.1 Hz, 2H), 8.15 (d, ^3J = 8.1 Hz, 2H), 7.99 (dd, ^3J = 8.1, 8.1 Hz, 2H), 4.50 (q, ^3J = 7.1 Hz, 4H), 1.48 (t, ^3J = 7.1 Hz, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.16, 155.40, 147.72, 138.00, 125.38, 124.70, 61.92, 14.31 ppm. IR (ZnSn): 2974, 1732, 1699, 1578, 1472 cm^{-1}.

6,6′-Dicarboxy-2,2′-bipyridine acid (6).[15c] To a solution of 6,6′-bis(ethoxycarbonyl-2,2′-bipyridine **5** (5.7 g, 19.0 mmol), ethanol (196 mL) and sodium hydroxide (3.6 g, 89.0 mmol) was added. The reaction mixture was heated and refluxed for 1 day, after which the solution was poured into water (140 mL) and acidified with aqueous 6 N HCl until pH = 1~2. The white precipitate was filtered, washed with ethanol and air-dried to afford a white solid (4.4 g, 96% yield). mp: 288–289 °C (lit. dec. 286 °C; 288 °C).[19-20] ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (dd, ^3J = 7.7, 1.3 Hz, 2H), 8.14 (dd, ^3J = 7.7, 7.7 Hz, 2H), 8.09 (dd, ^3J = 7.7, 1.3 Hz, 2H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ 166.30, 154.82, 148.44, 139.35, 125.67, 124.50 ppm. IR (ZnSn): 2837, 2551, 1690, 1581, 1421 cm^{-1}.

2,2′-Bipyridine-6,6′-dicarbonyl chloride (7).[15a] 2,2′-Bipyridine-6,6′-dicarboxylic acid **6** (6.1 g, 24.9 mmol) was treated with distilled $SOCl_2$ (120 mL) at reflux for 17 h. Excess of

$SOCl_2$ was removed under reduced pressure to afford the acid chloride as a white solid (6.8 g, 97% yield). mp: 182–184 °C (lit. 177–178 °C).[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, ^3J = 7.8 Hz, 2H), 8.19 (d, ^3J = 7.7 Hz, 2H), 8.11 (dd, ^3J = 7.7, 7.7 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 216.70, 155.14, 148.25, 138.77, 126.31, 125.78 ppm. IR (ZnSn): 3201, 2733, 1728, 1613, 1428 cm^{-1}.

General procedure to prepare 2,2'-bipyridine-6,6'-dicarboxamide (8).[15a] To a solution of amino alcohol (5.34 mmol) and triethylamine (1.5 mL, 10.7 mmol) in distilled $CHCl_3$ (15 mL), the acid chloride **7** (0.5 g, 1.8 mmol) was added at 0 °C. The mixture was stirred for 2 days at room temperature and then distilled $SOCl_2$ (3.4 mL) was added dropwise. After stirring for 12 h excess of $SOCl_2$ was removed under reduced pressure to give a black oil, which was extracted with CH_2Cl_2 (3 x 80 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. Concentration gave black solid product which was purified by silica gel column to give the product (CH_2Cl_2/MeOH = 98:2).

***N*6,*N*6'-bis((*S*)-1-chloro-3-methylbutan-2-yl)-2,2'-bipyridine-6,6'-dicarboxamide (8a)**.[15a] White solid (4.6 g, 78% yield). mp 210 °C (lit. 210 °C).[15a] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, ^3J = 7.8 Hz, 2H), 8.35 (d, ^3J = 9.4 Hz, 2H), 8.28 (d, ^3J = 7.7 Hz, 2H), 8.06 (dd, ^3J =7.8, 7.8 Hz, 2H), 4.17–4.26 (m, 2H), 3.89 (dd, ^2J = 11.3 Hz, ^3J = 3.7 Hz 2H), 3.80 (dd, ^2J = 11.3 Hz, ^3J = 3.7 Hz, 2H), 2.12–2.24 (m, 2H), 1.09 (d, ^3J = 6.8 Hz, 6H), 1.06 (d, ^3J = 6.8 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.82, 153.68, 149.18, 138.72, 123.57, 122.89, 55.02, 46.84, 29.56, 19.46, 18.89 ppm. IR (ZnSn): 3279, 2961, 1655, 1579, 1562, 1517, 1469 cm^{-1}.

***N*6,*N*6'-bis((*S*)-1-chloro-3-phenylpropan-2-yl)-2,2'-bipyridine-6,6'-dicarboxamide (8b)**. Yellow solid (0.8 g, 79% yield). mp: 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, ^3J = 7.8 Hz, 2H), 8.43 (d, ^3J = 8.9 Hz, 2H), 8.28 (d, ^3J = 7.6 Hz, 2H), 8.07 (dd, ^3J = 7.7, 7.7 Hz, 2H), 7.34–7.39 (m, 8H), 7.26–7.33 (m, 2H), 4.66–4.76 (m, 2H), 3.76 (dd, ^2J = 11.1 Hz, ^3J = 4.9 Hz, 2H), 3.69 (dd, ^2J = 11.2 Hz, ^3J = 3.5 Hz, 2H), 3.20 (dd, ^2J = 13.8 Hz, ^3J = 5.6 Hz, 2H), 3.09 (dd, ^2J = 13.8 Hz, ^3J = 8.2 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.49, 153.57, 149.07, 138.65, 136.69, 129.51, 128.84, 127.03, 123.64, 122.83, 50.58, 46.27, 37.39 ppm. IR (ZnSn): 3293, 3028, 1734, 1650. 1579, 1517, 1454 cm^{-1}.

***N*6,*N*6'-bis((*S*)-1-chloro-4-methylpentan-2-yl)-2,2'-bipyridine-6,6'-dicarboxamide (8c)**. White solid (1.7 g, 78% yield). mp: 184–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (dd, ^3J = 7.9, 1.1 Hz, 2H), 8.27 (dd, ^3J = 7.7, 1.1 Hz, 2H), 8.24 (d, ^3J = 9.1 Hz, 2H), 8.06 (dd, ^3J = 7.8, 7.8 Hz, 2H), 4.55–4.63 (m, 2H), 3.87 (dd, ^2J = 11.1 Hz, ^3J = 3.6 Hz, 2H), 3.76 (dd, ^2J = 11.2 Hz, ^3J = 3.6 Hz, 2H), 1.68–1.77 (m, 4H), 1.56–1.68 (m, 2H), 1.01 (d, ^3J = 6.3 Hz, 6H), 0.99 (d, ^3J = 6.2 Hz,

6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.56, 153.62, 138.61, 123.60, 122.85, 122.79, 48.75, 47.65, 41.06, 24.88, 22.84, 22.38 ppm. IR (ZnSn): 3305, 2954, 1722, 1650, 1566, 1465 cm^{-1}.

***N*6,*N*6'-bis((2*S*,3*R*)-1-chloro-3-methylpentan-2-yl)-2,2'-bipyridine-6,6'-dicarboxamide (8d)**. Yellow solid (0.5 g, 62% yield). mp: 148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, ^3J = 7.9 Hz, 2H), 8.35 (d, ^3J = 9.8 Hz, 2H), 8.28 (d, ^3J = 7.7 Hz, 2H), 8.06 (dd, ^3J = 7.8, 7.8 Hz, 2H), 4.23–4.33 (m, 2H), 3.90 (dd, ^2J = 11.5 Hz, ^3J = 3.8 Hz, 2H), 3.83 (dd, ^2J = 11.5 Hz, ^3J = 3.8 Hz, 2H), 1.85–2.03 (m, 2H), 1.56–1.71 (m, 2H), 1.18–1.35 (m, 2H), 1.05 (d, ^3J = 6.7 Hz, 6H), 0.95 (t, ^3J = 7.4 Hz, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.66, 153.56, 149.10, 138.61, 123.50, 122.77, 53.61, 46.95, 35.77, 25.17, 15.38, 11.04 ppm. IR (ZnSn): 3313, 2962, 2874, 1722, 1652, 1579, 1462 cm^{-1}.

6,6′-Bis(4-(*S*)-isopropyloxazolin-2-y1)-2,2′-bipyridine (1a).[15a] To a solution of the *N*6,*N*6'-bis((*S*)-1-chloro-3-methylbutan-2-yl)-2,2'-bipyridine-6,6'-dicarboxamide **8a** (2 g, 4.4 mmol) in MeOH (110 mL), aqueous NaOH (6 N, 35 mL) was added. The mixture was then stirred 2 days at 40 °C. The reaction was monitored by TLC (CH_2Cl_2/MeOH 9:1). The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo to give a white solid. After recrystallization (ethyl acetate/hexane) the product was obtained as a white solid (1.6 g, 96% yield). mp: 184 °C (lit. 187 °C).[15a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (dd, ^3J = 7.9, 1.1 Hz, 2H), 8.12 (dd, ^3J = 7.8, 1.1 Hz, 2H), 7.91 (dd, ^3J = 7.8 7.8 Hz, 2H), 4.55 (dd, ^3J = 9.6 Hz, ^2J = 8.2 Hz, 2H), 4.22 (dd, ^3J = 8.2 Hz, ^2J = 8.2 Hz, 2H), 4.16–4.22 (m, 2H), 1.88–1.96 (m, 2H), 1.09 (d, ^3J = 6.8 Hz, 6H), 0.97 (d, ^3J = 6.8 Hz, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.66, 155.34, 146.27, 137.53, 124.38, 123.53, 72.97, 70.79, 32.79, 19.12, 18.19 ppm. IR (ZnSn): 2953, 2864, 1636, 1577, 1474, 1445, 1263 cm^{-1}.

6,6′-Bis(4-(*S*)-benzyloxazolin-2-y1)-2,2′-bipyridine (1b). To a solution of the *N*6,*N*6'-bis((*S*)-1-chloro-3-phenylpropan-2-yl)-2,2'-bipyridine-6,6'-dicarboxamide **8b** (0.3 g, 0.6 mmol) in CH_2Cl_2 (5.5 mL), aqueous NaOH (6 N, 3.4 mL) was added. The mixture was stirred 7 days at 40 °C. The reaction was monitored by TLC (CH_2Cl_2/MeOH 9:1). The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo to give a brown solid. After recrystallization (ethyl acetate/hexane) the product was obtained as a yellow solid (1.5 g, 91% yield). mp: 206–208 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (dd, ^3J = 7.8, 1.1 Hz, 2H), 8.12 (dd, ^3J = 7.8, 1.1 Hz, 2H), 7.94 (dd, ^3J = 7.8, 7.8 Hz, 2H), 7.32–7.36 (m, 4H), 7.24–7.30 (m, 6H), 4.66–4.75 (m, 2H), 4.49 (dd, ^3J = 9.4 Hz, ^2J = 8.5 Hz, 2H), 4.29 (dd, ^2J = 8.5 Hz, ^3J = 7.6 Hz, 2H), 3.35 (dd, ^2J = 13.8 Hz, ^3J = 5.0 Hz, 2H), 2.80 (dd, ^2J = 13.8 Hz, ^3J = 9.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.12, 155.34, 146.17, 137.76, 137.62, 129.17, 128.54, 126.53, 124.40, 123.55, 72.39, 68.09, 41.64 ppm. IR

(ZnSn): 3274, 2884, 1657, 1577, 1444, 1368 cm^{-1}.

6,6′-Bis(4-(*S*)-isobutyloxazolin-2-y1)-2,2′-bi-pyridine (1c). To a solution of the *N*6,*N*6'-bis((*S*)-1-chloro-4-methylpentan-2-yl)-2,2'-bipy-ridine-6,6'-dicarboxamide **8c** (0.5 g, 1.1 mmol) in THF (11 mL, 0.1 M), NaH (0.1 g, 4.24 mmol) was added. The mixture was then stirred 7 days at room temperature under argon atmosphere. The reaction was monitored by TLC (CH_2Cl_2/MeOH 9:1). The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, to afford a brownish solid. After recrystallization (ethyl acetate/hexane) the product was obtained as a white solid (0.35 g, 80% yield). mp: 134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, ^3J = 7.9 Hz, 2H), 8.10 (dd, ^3J = 7.8, 1.1 Hz, 2H), 7.92 (dd, ^3J = 7.8, 7.8 Hz, 2H), 4.65 (dd, ^3J = 9.5 Hz, ^2J = 8.1 Hz, 2H), 4.41–4.48 (m, 2H), 4.14 (dd, ^3J = 8.1 Hz, ^2J = 8.1 Hz, 2H), 1.84–1.92 (m, 2H), 1.78–1.84 (m, 2H), 1.42–1.48 (m, 2H), 1.02 (d, ^3J = 6.6 Hz, 6H), 1.00 (d, ^3J = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.08, 154.95, 146.06, 137.10, 124.00, 123.02, 73.22, 65.09, 45.15, 25.13, 22.82, 22.61 ppm. IR (ZnSn): 2953, 2924, 1632, 1577, 1380 1279 cm^{-1}.

6,6′-Bis(4-(*S*)-secbutyloxazolin-2-y1)-2,2′-bi-pyridine (1d). To a solution of the *N*6,*N*6'-bis((2*S*,3*R*)-1-chloro-3-methylpentan-2-yl)-2,2'-bipyridine-6,6'-dicarboxamide **8d** (1.4 g, 2.9 mmol) in THF (30 mL, 0.1 M), NaH (0.3 g, 11.9 mmol) was added. The mixture was stirred 7 days at room temperature under argon atmosphere. The reaction was monitored by TLC (CH_2Cl_2/MeOH 9:1). The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated to give a brownish solid. After recrystallization (ethyl acetate/hexane) the product was obtained as a white solid (1.0 g, 85% yield). mp: 150–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, ^3J = 7.9 Hz, 2H), 8.12 (dd, ^3J = 7.7, 1.1 Hz, 2H), 7.91 (dd, ^3J = 7.8, 7.8 Hz, 2H), 4.54 (dd, ^3J = 9.3 Hz, ^2J = 8.0 Hz, 2H), 4.30–4.36 (m, 2H), 4.28 (dd, ^3J = 8.2 Hz, ^2J = 8.0 Hz, 2H), 1.75–1.85 (m, 2H), 1.65–1.74 (m, 2H), 1.24–1.35 (m, 2H), 0.99 (t, ^3J = 7.5 Hz, 6H), 0.92 (d, ^3J = 6.8 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.39, 155.18, 146.23, 137.33, 124.22, 123.30, 71.33, 70.13, 38.95, 26.03, 14.30, 11.41 ppm. IR (ZnSn): 2959, 2876, 1657, 1577, 1445, 1381 cm^{-1}.

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