

Trinuclear Non-Heme Iron Complexes Based on 4-Substituted 2,6-Diacylpyridine Ligands as Catalysts in Aerobic Allylic Oxidations

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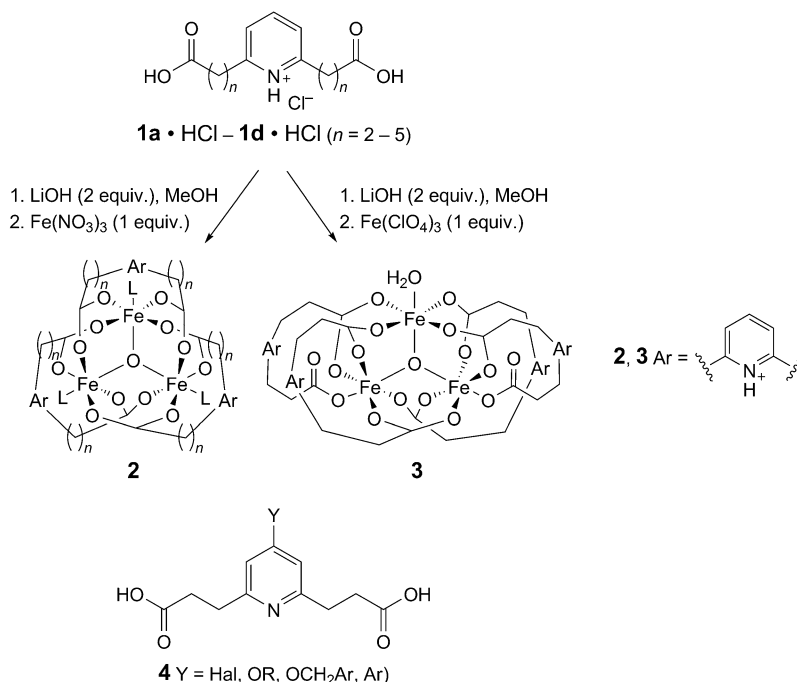
Taking the regio- and chemoselectivities of our iron complex precursors with pyridine core in aerobic oxidations into account, we envisioned a more effective influence on catalytic properties by the introduction of different substituents in 4-position of the pyridine moiety. The synthesis of these novel 4-substituted (pyridine-2,6-diyl)dipropionic acids **4** is described. Analogously to the unsubstituted derivative, ligands **4** reacted with $\text{Fe}(\text{ClO}_4)_3$ to form trinuclear $\text{Fe}_3(\mu_3\text{-O})$ complexes **3**, which were tested in the aerobic *Gif*-type oxidation of α -pinene to myrtenol, verbenone, myrtenal, and pinene oxide. The electronic nature of the substituents was found to slightly effect the ratio of allylic oxidation/epoxidation, whereas its influence on the oxidation preference of secondary to primary C–H bonds is negligible as compared to the unsubstituted complex.

Introduction. – Selective catalytic oxidations of hydrocarbons under mild conditions with molecular O_2 are an attractive goal in the field of oxidation catalysis, and many groups have made significant contributions to this research area [1–8]. In particular, non-heme iron complexes have been intensively investigated, stimulated by the fact that oxidizing enzymes such as methane monooxygenase [9], ribonucleotide reductase [10][11], stearoyl Δ^9 -ACP desaturase, and toluene monooxygenase [12] possess non-heme iron active sites, and a detailed understanding of the mechanisms should allow biomimetic oxidations in a preparative scale [13–20]. Pioneering work on aerobic oxidations was done by Barton and co-workers. The so-called *Gif*-type oxidations employ a trinuclear μ -oxo iron catalyst $\text{Fe}_3(\mu_3\text{-O})(\text{OAc})_6\text{L}_3$ ($\text{L} = \text{py}, \text{H}_2\text{O}$) in the presence of a reducing agent under 1 atm of O_2 in pyridine/AcOH [21–23].

We have recently developed a set of 2,6-diacylpyridine ligands **1** with different spacer lengths between the carboxylic acid and pyridine moieties, which were converted to the corresponding trinuclear $[\text{Fe}_3(\mu_3\text{-O})]$ complexes **2** or **3** depending on the type of counterion (*Scheme 1*) [24].

When complexes **2** or **3** were submitted to catalytic aerobic *Gif*-type oxidations of cyclohexane, α -pinene, and adamantane, it turned out that the catalytic properties, *i.e.*, turnover numbers, and regio- and chemoselectivities were only influenced to a minor extent by the chain lengths of the tether and by the type of counterion. In particular, the tether length had no influence on the nuclearity of the Fe complex. Furthermore, during catalytic aerobic oxidation, freeze-quench Mössbauer and nuclear inelastic scattering data revealed that the precursor complexes **2** and **3** undergo cleavage to mononuclear species [24][25], which is in agreement with Barton's original proposal of the catalytic cycle [21b]. We thus anticipated that substituents at C(4) of the pyridine

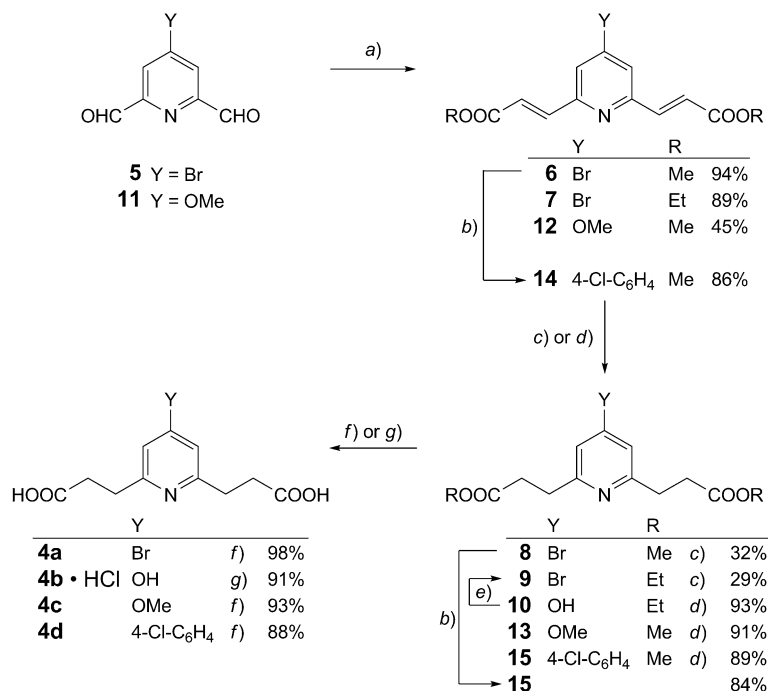
Scheme 1



ligand **4** should influence the steric, electronic, and catalytic properties of such a mononuclear species in a more effective way. The results towards this goal are reported below.

Results and Discussion. – The synthesis of 4-Br-substituted ligand **4a** commenced with the treatment of the known dicarbaldehyde **5** [26–28] with trimethyl phosphonoacetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and LiCl in MeCN at 0°, which provided α,β -unsaturated methyl ester **6** in 94% and ethyl ester **7** in 89% yield, respectively (Scheme 2). An X-ray crystal-structure analysis of **6** confirmed the (*E*)-configuration of the C=C bond¹). Initial attempts to convert the enoates **6** and **7** to the saturated diacetylpyridines **8** and **9**, respectively, by catalytic hydrogenation, according to our previously published procedure [24], were of limited success, because the use of Pd/C, Pd/BaSO₄, or PtO₂ resulted in reductive debromination prior to C=C bond hydrogenation. By using (AcO)₂Ni in the presence of 2 equiv. of NaBH₄ under 1 atm of H₂ in MeOH/AcOEt, the desired hydrogenation to **8** and **9** could be achieved, albeit with low yields of 32 and 29%, respectively. Even under these conditions, the

¹) The data for the X-ray analysis are available as supplementary material from the corresponding author. For compound **6**, CCDC-818683 contains the crystallographic data. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

Scheme 2. Synthesis of Ligands **4a–4d**

a) (MeO)₂P(O)CH₂COOR, DBU, LiCl, MeCN, 0° → r.t., 19 h. b) 4-Cl-C₆H₄-B(OH)₂, Pd(PPh₃)₄, K₂CO₃, KF, DME, H₂O, 95°, 48 h. c) (AcO)₂Ni, NaBH₄ (2 equiv.), H₂ (1 atm), MeOH, AcOEt, r.t., 15 min. d) Pd/C, H₂ (1 atm), MeOH, 60°, 15 h. e) POBr₃, toluene, 110°, 10 h; 20%. f) Dowex A, H₂O, 100°, 72 h. g) HCl, H₂O, 100°, 24 h.

reaction progress must be carefully monitored, and the reactions have to be stopped at incomplete conversion in order to avoid overreduction. As an alternative route, the 4-OH diester **10** (see below) was treated with POBr₃ in toluene at 110° to yield **9**, however, in only 20% yield. To get access to the free ligand **4a**, compound **8** was treated with Dowex A basic ion-exchange resin in refluxing H₂O, followed by washing with AcOH, and the free acid **4a** was isolated in 98% yield.

The corresponding 4-OH-substituted ligand **4b** was obtained as the hydrochloride **4b · HCl** in 91% yield from **10** by acidic hydrolysis (Scheme 2). Compound **4b · HCl** gave crystals suitable for X-ray crystal-structure analysis²⁾.

4-Methoxypyridine-2,6-dicarbaldehyde (**11**) [29] was submitted to a Horner–Wadsworth–Emmons olefination as described above to yield the α,β-unsaturated ester **12** in 45%, followed by catalytic hydrogenation with Pd/C to obtain **13** in 91%

²⁾ The data for the X-ray analysis are available as supplementary material from the corresponding author. For compound **4b · HCl**, CCDC-818688 contains the crystallographic data. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

yield. Final saponification with *Dowex A* gave the 4-MeO-substituted ligand **4c** in 93% yield (*Scheme 2*).

The 4-Br substituted bis(enoate) **6** was submitted to a *Suzuki* cross-coupling with (4-chlorophenyl)boronic acid, 5 mol-% of Pd(PPh₃)₄, K₂CO₃, KF, 1,2-dimethoxyethane (DME), and H₂O at 95° to yield the 4-(4-chlorophenyl)pyridine derivative **14** in 86% yield (*Scheme 2*). X-Ray crystal-structure analysis revealed the (*E*)-configuration for both of the C=C bonds and a dihedral angle of 24.0(3)° and 15.7(3)° (1:1 disorder), respectively, between the two aryl rings³). Subsequent catalytic hydrogenation of **14** provided diester **15** in 89% yield, which was also available *via* a *Suzuki* cross coupling of **8** under the above mentioned conditions in 84% yield. Saponification of diester **15** with *Dowex A* in MeOH gave the desired dicarboxylic acid **4d** in 88%.

The dimethyl ester of chelidamic acid, **16** [30], was treated with 1-bromo-4-(bromomethyl)benzene and K₂CO₃ in refluxing MeCN to give **17** in 75% yield (*Scheme 3*). Reduction of **17** with NaBH₄ gave the diol **18** in 32%. For both diester **17** and the corresponding diol **18**, X-ray crystal-structure analyses could be performed⁴). Diol **18** was oxidized with SeO₂ to the dicarbaldehyde **19** in 84% yield followed by *Horner–Wadsworth–Emmons* olefination to the α,β -unsaturated ester **20** in 67% yield, of which X-ray crystal structure could also be obtained⁵). However, upon catalytic hydrogenation, debenzoylation was observed, and diethyl 3,3'-(4-hydroxypyridine-2,6-diyl)dipropionate (**10**) was isolated in 93% yield. Therefore, compound **10** was treated again with 1-bromo-4-(bromomethyl)benzene and K₂CO₃ to give **21** in 84% yield, which was saponified with *Dowex A* to ligand **4e** in 94% yield.

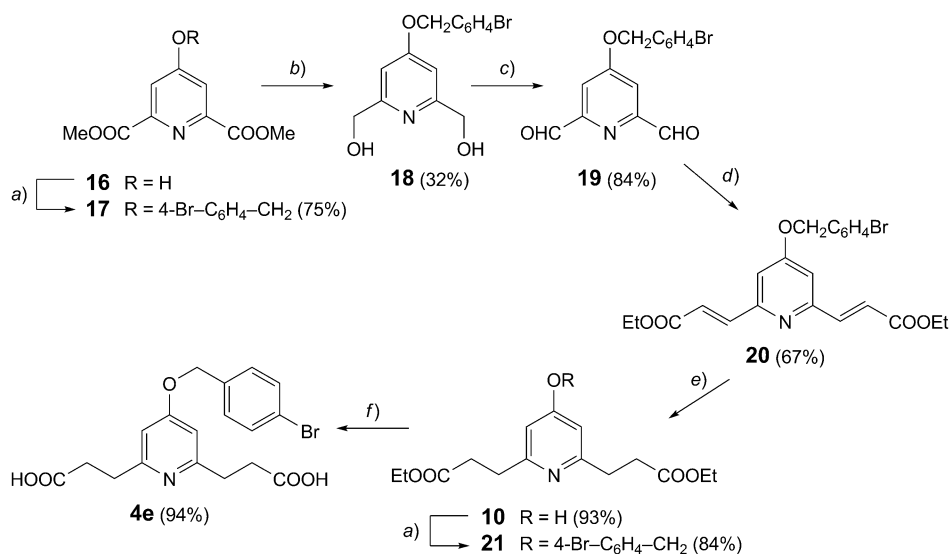
Having the ligands **4a–4e** in hand, the corresponding iron complexes **3** were prepared by deprotonation of **4** with LiOH in MeOH/CHCl₃ and subsequent treatment with Fe(ClO₄)₃·6 H₂O in 38–69% yield. The 4-OH-substituted ligand **4b** could not be converted to the iron complex **3b** (*Scheme 4*). Presumably, the phenolate moiety interferes with the complex formation. Unfortunately, X-ray crystal structures of the complexes **3a** and **3c–3e** could not be obtained. However, spectroscopic and analytical data (ESI-MS, IR, and elemental analysis) were in good agreement with our previously reported [Fe₃(μ_3 -O)] complex **3f** (R = H) [24].

The catalytic properties of precursor complexes **3a** and **3c–3e** were studied in the *Gif*-type oxidation of α -pinene (**22**). The results are summarized in *Scheme 5* and the *Table*. For comparison, the known complex **3f** (R = H) with an unsubstituted pyridine moiety was studied as well [24]. The aerobic oxidations yielded the four products myrtenol (**23**), verbenone (**24**), myrtenal (**25**), and α -pinene oxide (**26**) albeit with very

³) The data for the X-ray analysis are available as supplementary material from the corresponding author. For compound **14**, CCDC-818684 contains the crystallographic data. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

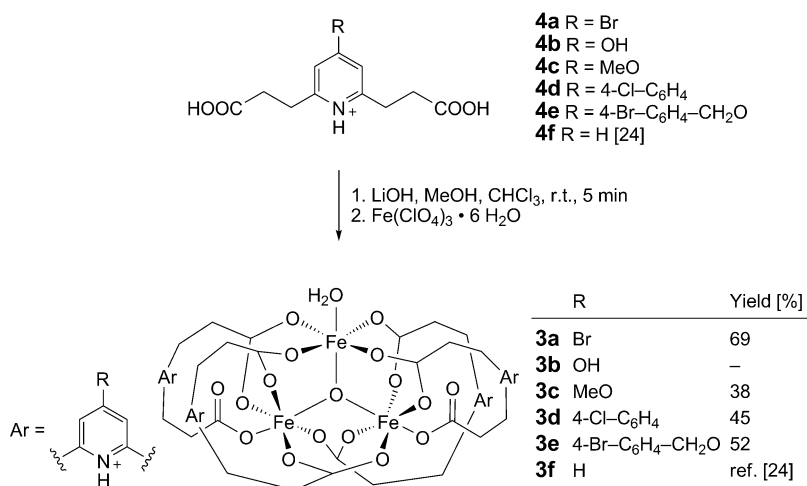
⁴) The data for the X-ray analyses are available as supplementary material from the corresponding author. For compounds **17** and **18**, CCDC-818685 and CCDC-818687, resp. contain the crystallographic data. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

⁵) The data for the X-ray analysis are available as supplementary material from the corresponding author. For compound **20**, CCDC-818686 contains the crystallographic data. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Scheme 3. Synthesis of Ligand **4e**

a) 4-Br-C₆H₄-CH₂Br, K₂CO₃, MeCN, 82°, 20 h. b) NaBH₄, MeOH, 0° → 68°, 17 h. c) SeO₂, dioxane, 95°, 20 h. d) (EtO)₂P(O)CH₂COOEt, DBU, LiCl, MeCN, 0° → r.t., 20 h. e) Pd/C, 1 atm H₂, MeOH, 60°, 17 h. f) Dowex A, H₂O, 100°, 72 h.

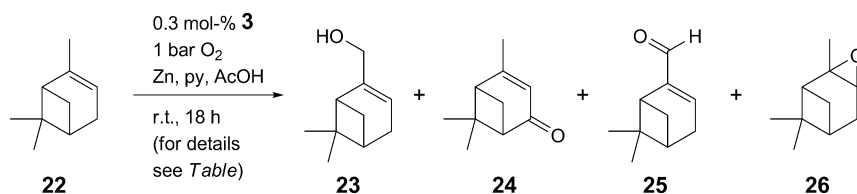
Scheme 4



poor conversion of the starting material⁶⁾). Irrespective of the substituent on the pyridine ligand in iron complexes **3a** and **3c–3f**, **24** was the major product, and the

⁶⁾ In contrast to catalytic *Gif*-type oxidations of adamantane with complex **3f**, where formation of adamantylpyridines *via* radical reaction was the major pathway (see [24]), the corresponding by-products could not be observed in the pinene oxidation.

Scheme 5

Table. Product Ratios in Catalytic Oxidations of α -Pinene (**22**) under Gif-Type Conditions^{a)}

Entry	Catalyst precursor	Yield [%]				Ox.:Epox. ^{b)} (23–25)/ 26	C ¹ :C ² (23+25)/ 24	TON ^{c)}
		23	24	25	26			
1	3a	0.1	1.6	0.1	0.5	78:22	11:89	7
2	3c	0.1	3.1	0.2	1.4	62:38	13:87	13
3	3d	0.1	2.0	0.2	0.8	74:26	13:87	9
4	3e	0.1	1.1	0.1	0.5	72:28	15:85	5
5	3f^{d)}	0.1	2.4	0.4	0.7	81:19	17:83	10

^{a)} Reaction conditions according to Scheme 5. ^{b)} Product ratios were determined by capillary GC by adding a defined amount of **23** as an external standard according to ref. [24]. ^{c)} TONs (turnover numbers) were calculated as follows: total amount of product [mol] per catalyst [mol]. ^{d)} Complex **3f** was prepared according to [24].

other allylic oxidation products, **23** and **25**, were only obtained as minor products in a ratio of 1:5 to 1:10 relative to **24**.

The ratio of allylic oxidation to epoxidation (*i.e.*, (**23–25**)/**26**) is only slightly influenced by the electronic properties of the pyridine moiety in the respective ligands. Whereas iron complexes **3a** and **3f** with the 4-Br-substituted pyridine and the unsubstituted pyridine ligand, respectively, revealed a pronounced preference of 78:22 and 81:19, towards allylic oxidation, respectively, the ratio decreased with the use of the iron complexes **3c** and **3e** with electron-donating substituents at the ligands, and it was lowest when the 4-MeO-substituted pyridine complex **3c** was applied. In contrast, the preferential oxidation of secondary C–H bonds as compared to primary C–H bonds was influenced only to a minor extent by the substituent, and the ratio ranged between 11:89 for **3a** and 17:83 for **3f**. In addition, the turnover number did not change significantly, and no clear tendency could be observed with regard to the different ligands.

Conclusions. – A series of 4-substituted 2,6-diacetylpyridine ligands **4a–4e** has been synthesized and converted to the corresponding trinuclear $[Fe_3(\mu_3-O)]$ complexes **3a** and **3c–3e**. The new complexes **3** were compared with complex **3f** bearing a 4-unsubstituted pyridine ligand [24]. Complexes **3** were employed for the catalytic Gif-type oxidation of α -pinene (**22**) to the allylic oxidation products myrtenol (**23**), verbenone (**24**), myrtenal (**25**), and the epoxide α -pinene oxide (**26**). The type of substituent at the pyridine moiety in the ligands seemed to have only a slight influence on the chemoselectivity, and the regioselectivity and activity, *i.e.*, turnover number

(TON), showed no dependency on the substituents. In general, allylic oxidation products **23–25** were favored over epoxide **26** by a 62:38 to 81:19 ratio. The strongest differentiation was found for ligands **4a** and **4f**, with a 4-Br-substituted and unsubstituted pyridine moiety, respectively. Allylic oxidation of secondary vs. primary C–H bonds was favored by 85:15 to 89:11. The X-ray crystal-structure analysis of complex **3f** with 4-unsubstituted pyridine ligands [24] revealed that the pyridine N-atom is protonated and thus is not involved in any binding interaction with the iron center. However, in agreement with Barton's mechanistic scenario [31][32], we propose that the trinuclear complex decomposes to a mononuclear species, in which the external pyridine competes with the 2,6-diacylpyridine as N-donor ligand⁷⁾. Even if the 4-substituent exerts some influence on the donor properties of the 2,6-diacylpyridine moiety, these effects are 'diluted' by the large excess of pyridine solvent. Thus, to study substituent effects more efficiently, the external pyridine must be replaced at least partially by electronically modified pyridine derivatives. With respect to preparative applications, our results indicate that trinuclear non-heme iron complexes are less amenable to optimization of catalytic properties. Therefore, future research on catalytic aerobic oxidations should be directed to mononuclear iron complexes.

Generous financial support by the *Deutsche Forschungsgemeinschaft* (SFB 706) and the *Ministerium für Wissenschaft, Forschung und Kunst des Landes Baden-Württemberg* is gratefully acknowledged.

Experimental Part

General. Column chromatography (CC): silica gel 60 (SiO₂; 40–63 µm; *Fluka*). Melting points (M.p.): *Büchi 510*; uncorrected. IR Spectra: *Bruker Vektor 22* FT-IR spectrophotometer; in cm⁻¹. ¹H- and ¹³C-NMR Spectra: *Bruker ARX 500* instrument; at 500/125 MHz; δ in ppm, *J* in Hz; signal assignments are based on DEPT-135 experiments. MS: *Finnigan MAT 95*, *Varian MAT 711*, and *Bruker Daltonics micrOTOF-Q* spectrometers; in *m/z* (rel. %).

General Procedure for the Horner–Wittig–Emmons Olefination of Pyridine-2,6-dicarbaldehydes **5, **11**, **19** (GP 1).** To a soln. of LiCl (4 equiv.) in MeCN (6 ml) were added methyl (dimethoxyphosphoryl)acetate, ethyl (dimethoxyphosphoryl)acetate, or ethyl (diethoxyphosphoryl)acetate (4 equiv.) and DBU (= 1,8-diazabicyclo[5.4.0]undec-7-ene; 3.8 equiv.), and the mixture was stirred at 0° for 20 min. Then was added dropwise a soln. of the respective pyridine-2,6-dicarbaldehyde (1 equiv.) in MeCN (7.5 ml), and stirring was continued at 0° for 1.5 h and at r.t. for 18 h. The mixture was filtered through SiO₂, the solvent was evaporated, and the residue was purified by CC (hexanes/AcOEt 1:2).

Dimethyl (2E,2'E)-3,3'-(4-Bromopyridine-2,6-diyl)bisprop-2-enoate (6**).** According to GP 1, from **5** (263 mg, 1.23 mmol). Yield 376 mg (1.15 mmol, 94%). Colorless solid. M.p. 146°. *R*_f (hexanes/AcOEt 1:2) 0.67. IR (ATR): 3066, 2948, 2841, 1711, 1643, 1547, 1434, 1395, 1326, 1302, 1222, 1192, 1154, 1119, 1042, 1010, 982, 864, 825. ¹H-NMR (500 MHz, CDCl₃): 3.84 (s, 2 MeO); 7.04 (*d*, *J* = 15.6, 2 H–C(2')); 7.52 (*s*, H–C(3), H–C(5)); 7.59 (*d*, *J* = 15.6, 2 H–C(1')). ¹³C-NMR (125 MHz, CDCl₃): 52.0 (MeO); 124.2 (C(2')); 127.5 (C(3), C(5)); 134.0 (C(4)); 141.6 (C(1')); 154.1 (C(2), C(6)); 166.7 (C=O). GC/EI-MS: 328 (39, [*M* + H]⁺), 326 (38, [*M* + H]⁺), 297 (60, [*M* + H – MeO]⁺), 295 (62, [*M* + H – MeO]⁺), 269 (64, [*M* + H – COOMe]⁺), 248 (16, [*M* + H – Br]⁺), 234 (46), 210 (100, [*M* + H – 2 COOMe]⁺), 208 (100, [*M* + H – 2 COOMe]⁺), 162 (16), 103 (40), 75 (36). Anal. calc. for C₁₃H₁₂BrNO₄ (326.14): C 47.87, H 3.71, N 4.29; found: C 48.02, H 3.81, N 4.20.

⁷⁾ Due to similar product ratio and low TON for complexes **3a** and **3c–3e**, we assume a mechanistic scenario comparable to the formation of complex **3f** with 4-unsubstituted ligand. In this case, the formation of mononuclear species during catalysis was derived from freeze-quench Mössbauer and neutron inelastic scattering (NIS) experiments. For details, see [24][25].

Diethyl (2E,2'E)-3,3'-(4-Bromopyridine-2,6-diyl)bisprop-2-enoate (7). According to *GP 1*, from **5** (561 mg, 2.62 mmol). Yield 826 mg (2.33 mmol, 89%). Colorless solid. M.p. 102°. R_f (hexanes/AcOEt 1:2) 0.68. IR (ATR): 3066, 2979, 2930, 2904, 2870, 1707, 1643, 1553, 1445, 1401, 1366, 1325, 1296, 1222, 1154, 1121, 1038, 986, 971, 864, 832, 811, 758, 694, 626, 615, 541. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.28 (t , $J = 7.1$, 2 MeCH_2); 4.22 (q , $J = 7.1$, 2 MeCH_2); 6.97 (d , $J = 15.6$, 2 $\text{H-C}(2')$); 7.45 (s , $\text{H-C}(3)$, $\text{H-C}(5)$); 7.51 (d , $J = 15.6$, 2 $\text{H-C}(1')$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 14.2 (MeCH_2); 60.9 (MeCH_2); 124.6 ($\text{C}(2')$); 127.4 ($\text{C}(3)$, $\text{C}(5)$); 134.0 ($\text{C}(4)$); 141.3 ($\text{C}(1')$); 154.2 ($\text{C}(2)$, $\text{C}(6)$); 166.3 (C=O). ESI-MS: 731.0 ($[2M + \text{Na}]^+$), 683.1, 623.1, 554.5, 517.2, 474.0, 396.0/394.0 ($[M + \text{Na} + \text{H}_2\text{O}]^+$), 378.0/376.0 ($[M + \text{Na}]^+$), 356.0/354.0 ($[M + \text{H}]^+$), 328.1, 301.1, 288.1, 270.1, 248.1, 216.1, 156.0. HR-ESI-MS: 354.0349 ($[M + \text{H}]^+$, $\text{C}_{15}\text{H}_{17}^{79}\text{BrNO}_4^+$; calc. 354.0341).

Dimethyl (2E,2'E)-3,3'-(4-Methoxypyridine-2,6-diyl)bisprop-2-enoate (12). According to *GP 1*, from **11** (978 mg, 5.92 mmol). Yield 741 mg (2.67 mmol, 45%). Colorless solid. M.p. 161°. R_f (hexanes/AcOEt 1:2) 0.63. IR (ATR): 3069, 2953, 2852, 1708, 1644, 1580, 1557, 1459, 1439, 1418, 1358, 1274, 1200, 1165, 1153, 1039, 1002, 984, 860. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.83 (s , 2 MeOOC); 3.90 (s , MeO); 6.88 (s , $\text{H-C}(3)$, $\text{H-C}(5)$); 7.03 (d , $J = 15.7$, 2 $\text{H-C}(2')$); 7.62 (d , $J = 15.7$, 2 $\text{H-C}(1')$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 51.9 (MeOOC); 55.5 (MeO); 110.8 ($\text{C}(3)$, $\text{C}(5)$); 122.9 ($\text{C}(2')$); 143.2 ($\text{C}(1')$); 154.4 ($\text{C}(2)$, $\text{C}(6)$); 167.0 ($\text{C}(4)$); 167.1 (C=O). ESI-MS: 318.1 ($[M + \text{Na} + \text{H}_2\text{O}]^+$), 300.1 ($[M + \text{Na}]^+$), 278.1 ($[M + \text{H}]^+$), 246.1 ($[M - \text{MeO}]^+$). HR-ESI-MS: 300.0841 ($[M + \text{Na}]^+$, $\text{C}_{14}\text{H}_{15}\text{NNaO}_5^+$; calc. 300.0848). Anal. calc. for $\text{C}_{14}\text{H}_{15}\text{NO}_5$ (277.27): C 60.64, H 5.45, N 5.05; found: C 60.42, H 5.48, N 4.97.

Diethyl (2E,2'E)-3,3'-(4-[(4-Bromobenzyl)oxy]pyridine-2,6-diyl)bisprop-2-enoate (20). According to *GP 1*, from **19** (494 mg, 1.54 mmol), with ethyl (diethoxyphosphoryl)acetate. Yield 478 mg (1.04 mmol, 67%). Colorless solid. M.p. 115°. R_f (hexanes/AcOEt 3:1) 0.40. IR (ATR): 3065, 2987, 2928, 2903, 2866, 1702, 1644, 1582, 1562, 1489, 1476, 1444, 1421, 1354, 1271, 1155, 1116, 1032, 996, 873, 856, 836, 803, 764, 702. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.35 (t , $J = 6.9$, 2 MeCH_2); 4.28 (q , $J = 6.9$, 2 MeCH_2); 5.1 (s , CH_2O); 6.9 (s , $\text{H-C}(3)$, $\text{H-C}(5)$); 7.0 (d , $J = 15.5$, 2 $\text{H-C}(2'')$); 7.29–7.30 (m , $\text{H-C}(2')$, $\text{H-C}(6')$ or $\text{H-C}(3')$, $\text{H-C}(5')$); 7.54–7.56 (m , $\text{H-C}(3')$, $\text{H-C}(5')$ or $\text{H-C}(2')$, $\text{H-C}(6')$); 7.6 (d , $J = 15.5$, 2 $\text{H-C}(1'')$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 14.3 (MeCH_2); 60.8 (MeCH_2); 69.4 (CH_2O); 111.3 ($\text{C}(3)$, $\text{C}(5)$); 122.6 ($\text{C}(4)$); 123.6 ($\text{C}(2'')$); 129.2 ($\text{C}(2')$, $\text{C}(6')$ or $\text{C}(3')$, $\text{C}(5')$); 132.0 ($\text{C}(3')$, $\text{C}(5')$ or $\text{C}(2')$, $\text{C}(6')$); 134.2 ($\text{C}(1'')$); 142.8 ($\text{C}(1'')$); 154.6 ($\text{C}(2)$, $\text{C}(6)$); 165.8 ($\text{C}(4)$); 166.6 (C=O). ESI-MS: 524.1, 502.1, 484.0/482.1 ($[M + \text{Na}]^+$), 462.1/460.0 ($[M + \text{H}]^+$), 359.2, 328.1, 301.1, 259.0, 247.1, 185.0, 143.0. HR-ESI-MS: 460.0735 ($[M + \text{H}]^+$, $\text{C}_{22}\text{H}_{23}^{79}\text{BrNO}_5^+$; calc. 460.0760).

General Procedure for the Suzuki Coupling of 4-Bromopyridines 6 and 8 (GP 2). To a soln. of **6** or **8** (1 equiv.) in 1,2-dimethoxyethane (DME)/ H_2O (28 ml, 10:1) were added sequentially (4-chlorophenyl)boronic acid (1.1 equiv.), K_2CO_3 (5 equiv.), KF (5 equiv.), and $\text{Pd}(\text{PPh}_3)_4$ (0.05 equiv.), and the mixture was stirred at 95° for 48 h. After cooling to r.t., the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (180 ml), washed with H_2O (3×80 ml), dried (MgSO_4), and evaporated. The crude product was purified by CC (hexanes/AcOEt).

Dimethyl (2E,2'E)-3,3'-(4-(4-Chlorophenyl)pyridine-2,6-diyl)bisprop-2-enoate (14). According to *GP 2*, from **6** (600 mg, 1.84 mmol). Yield 566 mg (1.58 mmol, 86%). Colorless solid. M.p. 154°. R_f (hexanes/AcOEt 4:1) 0.34. IR (ATR): 3066, 2949, 2837, 1706, 1640, 1600, 1541, 1495, 1433, 1389, 1260, 1239, 1224, 1187, 1095, 1057, 1032, 1011, 984, 974, 861, 817. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.85 (s , 2 MeO); 7.10 (d , $J = 15.6$, 2 $\text{H-C}(2')$); 7.48–7.50 (m , $\text{H-C}(2'')$, $\text{H-C}(6'')$ or $\text{H-C}(3'')$, $\text{H-C}(5'')$); 7.52 (s , $\text{H-C}(3)$, $\text{H-C}(5)$); 7.56–7.58 (m , $\text{H-C}(3'')$, $\text{H-C}(5'')$ or $\text{H-C}(2'')$, $\text{H-C}(6'')$); 7.73 (d , $J = 15.6$, 2 $\text{H-C}(1')$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 52.0 (MeO); 122.6 ($\text{C}(3)$, $\text{C}(5)$); 123.2 ($\text{C}(2')$); 128.3, 129.6 ($\text{C}(2'')$, $\text{C}(6'')$), $\text{C}(3'')$, $\text{C}(5'')$); 135.7, 135.9 ($\text{C}(1'')$, $\text{C}(4'')$); 142.8 ($\text{C}(1')$); 149.2 ($\text{C}(4)$); 153.7 ($\text{C}(2)$, $\text{C}(6)$); 167.1 (C=O). ESI-MS: 398.1 ($[M + \text{Na} + \text{H}_2\text{O}]^+$), 380.1 ($[M + \text{Na}]^+$), 358.1 ($[M + \text{H}]^+$), 246.1 ($[M - \text{Cl} - \text{C}_6\text{H}_4]^+$). HR-ESI-MS: 358.0828 ($[M + \text{H}]^+$, $\text{C}_{19}\text{H}_{17}\text{ClNO}_4^+$; calc. 358.0846). Anal. calc. for $\text{C}_{19}\text{H}_{16}\text{ClNO}_4$ (357.79): C 63.78, H 4.51, N 3.91; found: C 63.69, H 4.58, N 3.63.

Dimethyl 3,3'-(4-(4-Chlorophenyl)pyridine-2,6-diyl)dipropenoate (15). According to *GP 2*, from **8** (200 mg, 0.61 mmol). Yield 184 mg (0.51 mmol, 84%). Colorless solid. M.p. 32°. Following *GP 4*, from **14** (178 mg, 0.50 mmol) and Pd/C (15 mg). Yield 162 mg (0.45 mmol, 89%). R_f (hexanes/AcOEt 5:1) 0.23. IR (ATR): 2950, 1730, 1605, 1577, 1550, 1496, 1435, 1392, 1359, 1267, 1195, 1160, 1093, 1013, 988, 911, 877, 824, 730. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 2.83 (t , $J = 7.4$, 2 $\text{CH}_2(2'')$); 3.13 (t , $J = 7.4$, 2 $\text{CH}_2(1'')$); 3.68 (s , 2

MeO); 7.18 (br. s, H–C(3), H–C(5)); 7.42–7.45 (m, H–C(3''), H–C(5'')); 7.52–7.55 (m, H–C(2''), H–C(6'')). ¹³C-NMR (125 MHz, CDCl₃): 32.8, 32.9 (C(1'), C(2')); 51.6 (Me); 118.4 (C(3), C(5)); 128.3, 129.2 (C(2''), C(6''), C(3''), C(5'')); 135.0 (C(4'')); 137.1 (C(1'')); 147.9 (C(4)); 160.0 (C(2), C(6)); 173.7 (C=O). ESI-MS: 384.1 ([M + Na]⁺), 362.1 ([M + H]⁺), 330.1 ([M – MeO]⁺). HR-ESI-MS: 362.1161 ([M + H]⁺, C₁₉H₂₁ClNO₄⁺; calc. 362.1159).

General Procedure for the Reduction of 4-Bromopyridines 6 and 7 (GP 3). To a mixture of **6** or **7** (1 equiv.) and NaBH₄ (2 equiv.) was added a soln. of (AcO)₂Ni (1 equiv.) in MeOH/AcOEt (16 ml, 1:1), and the mixture was stirred under H₂ (1 atm) at r.t. for 15 min. After evaporation of the solvent, the residue was suspended in H₂O/CH₂Cl₂ (17 ml, 1:1), filtered, and the layers were separated. The aq. layer was extracted with CH₂Cl₂ (3 × 45 ml), the combined org. layers were dried (MgSO₄), evaporated, and the crude product was purified by CC (hexanes/AcOEt 5:1).

Dimethyl 3,3'-(4-Bromopyridine-2,6-diyl)dipropionate (8). According to GP 3, from **6** (1.00 g, 3.07 mmol). Yield 330 mg (1.0 mmol, 32%). Colorless solid. M.p. 67°. R_f (hexanes/AcOEt 5:1) 0.32. IR (ATR): 2951, 2847, 1732, 1647, 1563, 1435, 1365, 1300, 1247, 1195, 1160, 1031, 986, 857, 835, 805. ¹H-NMR (500 MHz, CDCl₃): 2.77 (t, J = 7.4, 2 CH₂(1')); 3.04 (t, J = 7.4, 2 CH₂(2')); 3.68 (s, 2 MeO); 7.19 (s, H–C(3), H–C(5)). ¹³C-NMR (125 MHz, CDCl₃): 32.4 (C(1')); 32.5 (C(2')); 51.6 (MeO); 123.8 (C(3), C(5)); 133.0 (C(4)); 160.7 (C(2), C(6)); 173.4 (C=O). ESI-MS: 332/330.0 ([M + H]⁺), 300.0/298.0 ([M – COOMe]⁺), 294.1, 286.1, 280.2, 250.1, 218.1. HR-ESI-MS: 330.0327 ([M + H]⁺, C₁₃H₁₇⁷⁹BrNO₄⁺; calc. 330.0341).

Diethyl 3,3'-(4-Bromopyridine-2,6-diyl)dipropionate (9). a) According to GP 3, from **7** (760 mg, 2.15 mmol). Yield 225 mg (0.63 mmol, 29%). Colorless oil. R_f (hexanes/AcOEt 5:1) 0.38.

b) To a suspension of **10** (443 mg, 1.50 mmol) in toluene (15 ml) was added POBr₃ (phosphoryl bromide; 850 mg, 2.96 mmol), and the mixture was refluxed for 10 h. After cooling to 0°, EtOH (15 ml) was added and the mixture was neutralized with sat. EtONa (in EtOH), filtered through SiO₂, and evaporated. The crude product was purified by CC (hexanes/AcOEt 5:1) to give **9** (109 mg, 0.30 mmol, 20%). Colorless oil. IR (neat): 2980, 2934, 1728, 1563, 1440, 1372, 1349, 1300, 1245, 1158, 1039, 1020, 945, 858, 789, 600. ¹H-NMR (500 MHz, CDCl₃): 1.24 (t, J = 7.2, 2 MeCH₂); 2.76 (t, J = 7.4, CH₂(2')); 3.04 (t, J = 7.4, CH₂(1')); 4.13 (q, J = 7.2, 2 MeCH₂); 7.19 (s, H–C(3), H–C(5)). ¹³C-NMR (125 MHz, CDCl₃): 14.2 (MeCH₂); 32.4 (C(2')); 32.9 (C(1')); 60.5 (MeCH₂); 123.8 (C(3), C(5)); 133.0 (C(4)); 160.8 (C(2), C(6)); 173.0 (C=O). ESI-MS: 360/358.1 ([M + H]⁺), 344.1, 328.0, 312.0, 280.2, 266.1, 234.1. HR-ESI-MS: 358.0659 ([M + H]⁺, C₁₅H₂₁⁷⁹BrNO₄⁺; calc. 358.0654).

General Procedure for the Catalytic Hydrogenation of Diacrylates 12, 14, and 20 (GP 4). To a suspension of the respective diacrylate **12**, **14**, or **20** in MeOH (70 ml) was added Pd/C (10%) and the mixture was heated under H₂ (1 atm) at 60° for 15 h. After filtration through SiO₂, the solvent was removed *in vacuo*.

Dimethyl 3,3'-(4-Methoxypyridine-2,6-diyl)dipropionate (13). According to GP 4, from **12** (629 mg, 2.27 mmol) and Pd/C (70 mg). Yield 581 mg (2.07 mmol, 91%). Colorless oil. R_f (hexanes/AcOEt 1:1) 0.19. IR (neat): 2951, 2846, 1732, 1596, 1574, 1463, 1435, 1364, 1259, 1192, 1147, 1065, 1040, 989, 856. ¹H-NMR (500 MHz, CDCl₃): 2.77 (t, J = 7.5, 2 CH₂(2')); 3.02 (t, J = 7.5, 2 CH₂(1')); 3.68 (s, 2 MeOOC); 3.80 (s, MeO); 6.54 (s, H–C(3), H–C(5)). ¹³C-NMR (125 MHz, CDCl₃): 32.9 (C(2')); 33.0 (C(1')); 51.6 (MeOOC); 55.0 (MeO); 106.5 (C(3), C(5)); 160.9 (C(2), C(6)); 166.3 (C(4)); 173.7 (C=O). EI-MS: 304.1 ([M + Na]⁺), 282.1 ([M + H]⁺), 250.1 ([M – MeO]⁺). HR-ESI-MS: 304.1159 ([M + Na]⁺, C₁₄H₁₉NNaO₅⁺; calc. 304.1161). Anal. calc. for C₁₄H₁₉NO₅ (281.30): C 59.78, H 6.81, N 4.98; found: C 59.61, H 6.88, N 4.93.

Diethyl 3,3'-(4-Hydroxypyridine-2,6-diyl)dipropionate (10). According to GP 4, from **20** (1.49 g, 3.25 mmol) was obtained a precipitate, which was recrystallized from CH₂Cl₂ to give **10** (892 mg, 3.02 mmol, 93%). Colorless solid. M.p. 106°. IR (ATR): 3421, 3257, 3090, 3046, 2911, 2796, 1717, 1626, 1480, 1449, 1417, 1376, 1354, 1297, 1284, 1179, 1161, 1056, 1021, 864, 788, 737. ¹H-NMR (500 MHz, MeOD): 1.23 (t, J = 7.2, 2 MeCH₂); 2.73 (t, J = 7.4, 2 CH₂(2')); 2.92 (t, J = 7.4, 2 CH₂(1')); 4.14 (q, J = 7.2, 2 MeCH₂); 6.30 (s, H–C(3), H–C(5)). ¹³C-NMR (125 MHz, MeOD): 14.5 (MeCH₂); 29.1 (C(2')); 33.6 (C(1')); 62.0 (MeCH₂); 114.3 (C(3), C(5)); 154.1 (C(2), C(6)); 173.4 (C=O); 180.8 (C(4)). ESI-MS: 332.2 ([M + H + 2 H₂O]⁺), 318.1 ([M + Na]⁺), 296.2 ([M + H]⁺), 250.1 ([M – EtO]⁺). HR-ESI-MS:

296.1487 ($[M + H]^+$, $C_{15}H_{22}NO_5^+$; calc. 296.1498). Anal. calc. for $C_{15}H_{21}NO_5 \cdot 0.3 CH_2Cl_2$ (323.64): C 56.90, H 6.75, N 4.33; found: C 57.11, H 6.80, N 4.47.

General Procedure for the Saponification of Esters 9, 13, 15, and 21 with Dowex A (GP 5). A suspension of the respective ester (0.66–2.35 mmol) and Dowex Marathon A® basic ion exchange resin (2.00 g) in H_2O (17 ml) was refluxed for 72 h. Then, the ion exchange resin was isolated by filtration, washed with MeOH, stirred with AcOH/ H_2O (1:1, 2×150 ml), removed by filtration and the filtrate was concentrated. The crude product was dried in a vacuum dessiccator over P_4O_{10} for 7 d.

3,3'-(4-Bromopyridine-2,6-diyl)dipropionic Acid (4a). According to GP 5, from **9** (366 mg, 1.02 mmol). The crude product was recrystallized from MeOH/ H_2O 3:1. Yield 301 mg (1.00 mmol, 98%). Colorless solid. M.p. 146°. IR (ATR): 3066, 2951, 2846, 1731, 1647, 1563, 1435, 1365, 1301, 1247, 1195, 1160, 1031, 986, 883, 857, 835, 805. 1H -NMR (500 MHz, D_2O): 2.82 (t , $J = 7.2$, 2 $CH_2(2')$); 3.21 (t , $J = 7.2$, 2 $CH_2(1')$); 7.89 (s , H–C(3), H–C(5)). ^{13}C -NMR (125 MHz, D_2O): 29.3 (C(1')); 33.7 (C(2')); 127.2 (C(3), C(5)); 141.7 (C(4)); 157.4 (C(2), C(6)); 177.8 (C=O). ESI-MS: 304.0/302.0 ($[M + H]^+$), 286.0/284.0 ($[M - OH]^+$), 258.2, 238.1, 222.1 ($[M - Br]^+$), 206.1. HR-ESI-MS: 302.0012 ($[M + H]^+$, $C_{11}H_{13}^{79}BrNO_4^+$; calc. 302.0028).

3,3'-(4-Methoxypyridine-2,6-diyl)dipropionic Acid (4c). According to GP 5, from **13** (661 mg, 2.35 mmol). Yield 555 mg (2.19 mmol, 93%). Colorless solid. M.p. 141°. IR (ATR): 2929, 2470, 1974, 1702, 1656, 1620, 1540, 1484, 1445, 1405, 1366, 1200, 1160, 939, 855, 822, 804, 708, 647. 1H -NMR (500 MHz, $(D_6)DMSO$): 2.61 (t , $J = 7.5$, 2 $CH_2(2')$); 2.87 (t , $J = 7.5$, 2 $CH_2(1')$); 3.78 (s , 2 MeOOC); 3.80 (s , MeO); 6.69 (s , H–C(3), H–C(5)). ^{13}C -NMR (125 MHz, $(D_6)DMSO$): 32.4 (C(1')); 32.8 (C(2')); 51.6 (MeOOC); 55.1 (MeO); 106.3 (C(3), C(5)); 160.8 (C(2), C(6)); 166.0 (C(4)); 174.0 (C=O). EI-MS: 253.1 (40, M^+), 236.1 (10, $[M - OH]^+$), 208.1 (100, $[M - COOH]^+$), 190.1 (36), 163.1 (24, $[M - 2 COOH]^+$), 148.1 (5), 135.1 (5), 119.1 (3), 106.1 (2), 91.1 (2), 77.0 (2), 65.1 (2), 44.0 (2). HR-ESI-MS: 276.0834 ($[M + Na]^+$, $C_{12}H_{15}NNaO_5^+$; calc. 276.0848).

3,3'-(4-(4-Chlorophenyl)pyridine-2,6-diyl)dipropionic Acid (4d). According to GP 5, from **15** (240 mg, 0.66 mmol). Yield 194 mg (0.58 mmol, 88%). Colorless solid. M.p. 157°. IR (ATR): 2930, 2470, 1974, 1702, 1656, 1620, 1541, 1484, 1445, 1405, 1366, 1316, 1200, 1160, 939, 855, 822, 804, 746, 708, 647, 589. 1H -NMR (500 MHz, $(D_6)DMSO$): 2.73 (t , $J = 7.4$, 2 $CH_2(2')$); 3.01 (t , $J = 7.4$, 2 $CH_2(1')$); 7.32 (br , s , H–C(3), H–C(5)); 7.37–7.48 (m , H–C(3''), H–C(5'')); 7.58–7.65 (m , H–C(2''), H–C(6'')). ^{13}C -NMR (125 MHz, $(D_6)DMSO$): 33.1, 33.8 (C(1'), C(2')); 118.9 (C(3), C(5)); 129.3, 129.6 (C(2''), C(6''), C(3''), C(5'')); 135.9 (C(4'')); 137.7 (C(1'')); 148.2 (C(4)); 160.3 (C(2), C(6)); 175.2 (C=O). ESI-MS: 334.1 ($[M + H]^+$), 279.1. HR-ESI-MS: 334.0836 ($[M + H]^+$, $C_{17}H_{17}ClNO_4^+$; calc. 334.0846).

3,3'-(4-(4-Bromobenzyl)oxy)pyridine-2,6-diyl)dipropionic Acid (4e). According to GP 5, from **21** (477 mg, 1.03 mmol). The crude product was recrystallized from MeOH/ $CHCl_3$ 1:1. Yield 396 mg (0.97 mmol, 94%). Colorless solid. M.p. 203°. IR (ATR): 2925, 2458, 1974, 1664, 1622, 1540, 1486, 1475, 1450, 1415, 1367, 1340, 1320, 1252, 1214, 1170, 1107, 1086, 1052, 1009, 965, 869, 852, 826, 800. 1H -NMR (500 MHz, $(D_6)DMSO$): 2.62 (t , $J = 7.5$, 2 $CH_2(2')$); 2.88 (t , $J = 7.5$, 2 $CH_2(1')$); 5.12 (s , CH_2O); 6.77 (s , H–C(3), H–C(5)); 7.41–7.42 (m , 2 H of H–C(2'), H–C(6'), H–C(3'), H–C(5')); 7.59–7.61 (m , 2 H of H–C(2''), H–C(6''), H–C(3''), H–C(5'')). ^{13}C -NMR (125 MHz, $(D_6)DMSO$): 32.3 (C(1'')); 32.7 (C(2'')); 68.2 (C(7)); 106.9 (C(3), C(5)); 121.2 (C(4'')); 128.5, 129.9 (C(2'), C(6'), C(3'), C(5')); 135.7 (C(1')); 160.9 (C(2), C(6)); 164.9 (C(4)); 173.9 (C=O). ESI-MS: 448.0/446.0 ($[M + K]^+$), 432.0/430.0 ($[M + Na]^+$), 422.1, 410.0/408.0 ($[M + H]^+$). HR-ESI-MS: 430.0252 ($[M + Na]^+$, $C_{18}H_{18}^{79}BrNO_5^+$; calc. 430.0266). Anal. calc. for $C_{18}H_{18}BrNO_5 \cdot 0.5 H_2O$ (417.25): C 51.81, H 4.59, N 3.36; found: C 51.81, H 4.45, N 3.34.

3,3'-(4-Hydroxypyridine-2,6-diyl)dipropionic Acid Hydrochloride (4b · HCl). A soln. of **10** (4.00 g, 13.5 mmol) in conc. HCl/ H_2O (1.5:1, 100 ml) was refluxed for 24 h. After evaporation of the solvent, the crude product was recrystallized from H_2O and dried in a vacuum dessiccator over P_4O_{10} for 7 d to give **4b · HCl** (3.41 g, 12.4 mmol, 91%). Colorless solid. M.p. 212°. IR (ATR): 3087, 2858, 2460, 1994, 1733, 1708, 1626, 1477, 1419, 1402, 1385, 1324, 1289, 1213, 1181, 1159, 1026, 930, 865, 783, 668, 563, 533. 1H -NMR (500 MHz, D_2O): 2.76 (t , $J = 7.2$, 2 $CH_2(2')$); 3.04 (t , $J = 7.2$, 2 $CH_2(1')$); 6.90 (s , H–C(3), H–C(5)). ^{13}C -NMR (125 MHz, D_2O): 27.6 (C(1')); 32.1 (C(2')); 111.2 (C(3), C(5)); 156.0 (C(2), C(6)); 171.3 (C(4)); 175.7 (C=O). ESI-MS: 262.1 ($[M + Na - HCl]^+$), 240.1 ($[M + H - HCl]^+$), 222.1 ($[M -$

HCl – OH]⁺). HR-ESI-MS: 240.0857 ([*M* + H – HCl]⁺, C₁₁H₁₄NO₅⁺; calc. 240.0872). Anal. calc. for C₁₁H₁₄ClNO₅ (275.69): C 47.92, H 5.12, Cl 12.86, N 5.08; found: C 47.74, H 5.08, Cl 12.64, N 4.97.

General Procedure for the Williamson Etherification of 4-Hydroxypyridines **16 and **10** (GP 6).** A suspension of K₂CO₃ (2–2.4 equiv.), the respective ester **16** or **10** (1 equiv.) and 1-bromo-4-(bromomethyl)benzene (1 equiv.) in MeCN (10–25 ml) was heated under reflux for 17 h. After cooling to r.t., the mixture was filtered and treated with ice water (10–25 ml). The resulting precipitate was isolated by filtration and recrystallized from toluene.

Dimethyl 4-[(4-Bromobenzyl)oxy]pyridine-2,6-dicarboxylate (17**).** According to GP 6, from **16** (771 mg, 3.65 mmol). Yield 1.04 g (2.74 mmol, 75%). Colorless solid. M.p. 161°. IR (ATR): 3089, 2949, 1739, 1716, 1592, 1493, 1437, 1348, 1250, 1230, 1187, 1161, 1106, 1026, 1002, 891, 880, 801, 795, 786. ¹H-NMR (500 MHz, CDCl₃): 4.02 (s, 2 MeO); 5.19 (s, CH₂O); 7.31–7.33 (m, 2 H of H–C(2'), H–C(6'), H–C(3'), H–C(5')); 7.55–7.56 (m, 2 H of H–C(2'), H–C(6'), H–C(3'), H–C(5')); 7.88 (s, H–C(3), H–C(5)). ¹³C-NMR (125 MHz, CDCl₃): 53.4 (MeO); 70.0 (CH₂O); 114.8 (C(3), C(5)); 122.9 (C(4')); 129.3, 132.1 (C(2'), C(6'), C(3'), C(5')); 133.7 (C(1')); 149.9 (C(2), C(6)); 165.1 (C=O); 166.5 (C(4)). ESI-MS: 404.0/402.0 ([*M* + Na]⁺), 382.0/380.0 ([*M* + H]⁺), 358.1. HR-ESI-MS: 380.0136 ([*M* + H]⁺, C₁₆H₁₅BrNO₅⁺; calc. 380.0134). Anal. calc. for C₁₆H₁₄BrNO₅ (380.19): C 50.55, H 3.71, N 3.68; found: C 50.34, H 3.82, N 3.63.

Diethyl 3,3'-[4-[(4-Bromobenzyl)oxy]pyridine-2,6-diyl]dipropionate (21**).** GP 6 and modified work-up: reaction of **10** (1.03 g, 3.49 mmol) gave a precipitate, which was isolated by filtration, and the filtrate was extracted with CHCl₃ (3 × 50 ml), dried (MgSO₄), and evaporated. The combined crude products were purified by CC (hexanes/AcOEt 2:1, then EtOH/CH₂Cl₂ 1:1). Yield 1.36 g (2.93 mmol, 84%). Colorless solid. M.p. 30°. IR (ATR): 2981, 2939, 2876, 1969, 1722, 1596, 1570, 1489, 1438, 1406, 1373s, 1268s, 1184s, 1144vs, 1009s, 989s, 942m, 862s, 846s, 806s, 718m, 668m, 606m. ¹H-NMR (500 MHz, MeOD): 1.23 (t, *J* = 7.2, 2 MeCH₂); 2.73 (t, *J* = 7.5, 2 CH₂(2'')); 3.01 (t, *J* = 7.5, 2 CH₂(1'')); 4.11 (q, *J* = 7.2, 2 MeCH₂); 5.14 (s, CH₂O); 6.78 (s, H–C(3), H–C(5)); 7.37–7.40 (m, 2 H of H–C(2'), H–C(6'), H–C(3'), H–C(5')); 7.55–7.58 (m, 2 H of H–C(2'), H–C(6'), H–C(3'), H–C(5')). ¹³C-NMR (125 MHz, MeOD): 14.6 (MeCH₂); 33.7 (C(1'')); 34.6 (C(2'')); 61.6 (MeCH₂); 70.1 (CH₂O); 108.7 (C(3), C(5)); 123.0 (C(4)); 130.6, 132.8 (C(2'), C(6'), C(3'), C(5')); 137.0 (C(1')); 162.7 (C(2), C(6)); 167.5 (C(4)); 174.6 (C=O). ESI-MS: 488/486.1 ([*M* + Na]⁺), 466/464.1 ([*M* + H]⁺), 418.1, 387/385.2 ([*M* – EtOOC(CH₂)₂]⁺), 171/169.0 ([Br – C₆H₄ – CH₂]⁺). HR-ESI-MS: 464.1067 ([*M* + H]⁺, C₂₂H₂₇⁷⁹BrNO₅⁺; calc. 464.1073). Anal. calc. for C₂₂H₂₆BrNO₅ (464.35): C 56.90, H 5.64, N 3.02; found: C 56.63, H 5.57, N 2.96.

4-[(4-Bromobenzyl)oxy]pyridine-2,6-diyl]dimethanol (18**).** To an ice-cooled suspension of **17** (3.11 g, 8.18 mmol) in MeOH (60 ml) was added portionwise NaBH₄ (1.49 g, 39.23 mmol), and the mixture was stirred at 0° for 1 h, at r.t. for 2 h, and under reflux for 14 h. After cooling to r.t., the solvent was evaporated, and the residue was treated with a soln. of K₂CO₃ (6.00 g) in H₂O (25 ml) and refluxed for 2 h. Then the mixture was continuously extracted with CH₂Cl₂ for 22 h. After removal of the solvent, **18** was isolated (870 mg, 2.69 mmol, 32%). Colorless solid. M.p. 152°. IR (ATR): 3300, 3093, 2894, 2844, 2716, 1601, 1573, 1489, 1445, 1433, 1353, 1310, 1220, 1150, 1090, 1070, 1032, 1001, 927, 870, 849, 804, 754, 676. ¹H-NMR (500 MHz, MeOD): 4.64 (s, 2 CH₂OH); 5.24 (s, CH₂O); 7.08 (s, H–C(3), H–C(5)); 7.44–7.46 (m, 2 H of H–C(2'), H–C(6'), H–C(3'), H–C(5')); 7.60–7.63 (m, 2 H of H–C(2'), H–C(6'), H–C(3'), H–C(5')). ¹³C-NMR (125 MHz, MeOD): 65.4 (CH₂); 70.2 (CH₂O); 106.7 (C(3), C(5)); 123.1 (C(4)); 130.9, 131.6 (C(2'), C(6'), C(3'), C(5')); 137.2 (C(1')); 164.2 (C(2), C(6)); 168.21 (C(4)). ESI-MS: 348.0/346.0 ([*M* + Na]⁺), 326.0/324.0 ([*M* + H]⁺), 171.0/169.0 ([Br – C₆H₄ – CH₂]⁺). HR-ESI-MS: 324.0209 ([*M* + H]⁺, C₁₄H₁₅⁷⁹BrNO₃⁺; calc. 324.0235).

4-[(4-Bromobenzyl)oxy]pyridine-2,6-dicarbaldehyde (19**).** To a suspension of **18** (600 mg, 1.88 mmol) in dioxane (10 ml) was added SeO₂ (216 mg, 1.95 mmol), and the mixture was heated at 95° for 20 h. After cooling to r.t. and filtration through SiO₂, the solvent was evaporated, and the crude product was purified by CC (CH₂Cl₂/AcOEt 1:3) to give **19** (507 mg, 1.59 mmol, 84%). Colorless solid. M.p. 122°. IR (ATR): 3077, 2847, 2856, 1705, 1678, 1593, 1557, 1487, 1459, 1445, 1385, 1367, 1316, 1278, 1210, 1192, 1163, 1071, 1050, 1009, 987, 949, 917, 882, 832, 800, 730, 703. ¹H-NMR (500 MHz, CDCl₃): 5.20 (s, CH₂O); 7.30–7.32 (m, 2 H of H–C(2'), H–C(6'), H–C(3'), H–C(5')); 7.54–7.56 (m, 2 H of H–C(2'), H–C(6'), H–C(3'), H–C(5')); 7.69 (m, H–C(3), H–C(5)); 10.11 (s, 2 CHO). ¹³C-NMR (125 MHz, CDCl₃): 70.16 (CH₂O); 111.7 (C(3), C(5)); 127.8 (C(4)); 129.5, 132.1 (C(2'), C(6'), C(3'), C(5')); 133.5

(C(1')); 154.9 (C(2), C(6)); 166.5 (C(4)); 192.2 (CHO). ESI-MS: 408.0/406.0 ($[M + Na + 2 MeOH]^+$), 376.0/374.0 ($[M + Na + MeOH]^+$), 344.0/342.0 ($[M + Na]^+$), 301.1, 286.0/284.0 ($[M + Na - 2 CHO]^+$). HR-ESI-MS: 341.9736 ($[M + Na]^+$), $C_{14}H_{10}^{79}BrNNaO_3^+$; calc. 341.9742).

Iron Complex $Fe_3(\mu_3-O)(4aH)_4(H_2O)(ClO_4)_3 \cdot 5 H_2O$ (3a**).** A soln. of **4a** (140 mg, 463 μ mol) and LiOH (23 mg, 958 μ mol) in MeOH (2 ml) was stirred at r.t. for 20 min. Then was added a soln. of $Fe(ClO_4)_3 \cdot x H_2O$ (164 mg, 463 μ mol) in MeOH (0.5 ml) and the mixture was stirred at r.t. for 5 min. The orange-red precipitate was isolated by filtration, dissolved in MeOH/ H_2O (2:1, 5 ml) and heated at reflux for 1 min. Slow evaporation of the solvent over three weeks gave **3a** (140 mg, 80 μ mol, 69% based on **4a**). Red solid. M.p. 238° (dec.). UV/VIS (H_2O): 271 (4.50). IR (ATR): 3529, 3293, 3084, 2951, 2768, 2013, 1606, 1560, 1489, 1436, 1401, 1366, 1311, 1200, 1165, 1077, 1004, 980, 949, 875, 851, 741, 678, 652, 620. ESI-MS: 1385.7 ($[C_{44}H_{42}Br_4Fe_3N_4O_{17}]^+$), 1362.8, 1316.9, 1100.74 ($[C_{33}H_{32}Br_3Fe_3N_3O_{14}]^+$), 1082.73, 680.93. HR-ESI-MS: 1381.7351 ($[M - 3 ClO_4 - H_2O]^+$), $C_{44}H_{44}Br_4Fe_3N_4O_{17}^+$; 1385.7286).

Attempted Synthesis of Iron Complex $Fe_3(\mu_3-O)(4bH)_4(H_2O)(ClO_4)_3 \cdot 5 H_2O$ (3b**).** A soln. of **4b** (200 mg, 790 μ mol) and LiOH (38 mg, 1.58 mmol) in MeOH (4 ml) was stirred at r.t. for 20 min. Then was added a soln. of $Fe(ClO_4)_3 \cdot x H_2O$ (280 mg, 791 μ mol) in MeOH (1.5 ml) and the mixture was stirred at r.t. for 5 min. However, no precipitate was obtained.

Iron Complex $Fe_3(\mu_3-O)(4cH)_4(H_2O)(ClO_4)_3 \cdot 5 H_2O$ (3c**).** A soln. of **4c** (200 mg, 790 μ mol) and LiOH (38 mg, 1.58 mmol) in MeOH (4 ml) was stirred at r.t. for 20 min. Then was added a soln. of $Fe(ClO_4)_3 \cdot x H_2O$ (280 mg, 791 μ mol) in MeOH (1.5 ml) and the mixture was stirred at r.t. for 5 min. The orange-red precipitate was isolated by filtration, dissolved in MeOH/ CH_2Cl_2 (1:3, 4 ml) and refluxed for 1 min. Slow evaporation of the solvent over 3 d gave **3c** (118 mg, 75 μ mol, 38% based on **4c**). Red solid. M.p. 247° (dec.). UV/VIS (H_2O): 270 (4.78). IR (ATR): 3529, 3293, 3084, 2951, 2768, 2013, 1606, 1560, 1489, 1436, 1401, 1366, 1311, 1200, 1165, 1077, 1004, 980, 949, 875, 851, 741, 678, 652, 620. ESI-MS: 955.0, 937.0, 595.57 ($[C_{48}H_{56}Fe_3N_4O_{21}]^{2+}$), 542.1, 514.5, 460.0, 316.0. HR-ESI-MS: 595.5705 ($[M - 3 ClO_4 - H_2O]^{2+}$), $[C_{48}H_{56}Fe_3N_4O_{21}]^{2+}$; calc. 596.0743).

Iron Complex $Fe_3(\mu_3-O)(4dH)_4(H_2O)(ClO_4)_3 \cdot 3 MeOH$ (3d**).** A soln. of **4d** (100 mg, 300 μ mol) and LiOH (14.5 mg, 604 μ mol) in MeOH (2 ml) and $CHCl_3$ (1 ml) was stirred at r.t. for 20 min. Then was added a soln. of $Fe(ClO_4)_3 \cdot x H_2O$ (106 mg, 300 μ mol) in MeOH (0.5 ml), and the mixture was stirred at r.t. for 5 min. The yellow precipitate was isolated by filtration, dissolved in MeOH/ $CHCl_3$ (1:4, 5 ml), and refluxed for 1 min. Slow evaporation of the solvent over 2 d gave **3d** (62 mg, 34 μ mol, 45% based on **4d**). Red solid. M.p. 228° (dec.). UV/VIS (H_2O): 271 (4.65). IR (ATR): 3301, 2972, 1716, 1628, 1594, 1544, 1488, 1441, 1402, 1365, 1315, 1229, 1170, 1058, 1011, 978, 882, 830, 809, 733, 669, 619, 556. ESI-MS: 1512.1 ($[C_{68}H_{58}Cl_4Fe_3N_4O_{17}]^+$), 1480.0, 1197.0 ($[C_{51}H_{44}Cl_3Fe_3N_3O_{14}]^+$), 1179.0 ($[C_{51}H_{42}Cl_3Fe_3N_3O_{13}]^+$), 1164.9, 1103.0, 954.0. HR-ESI-MS: 1510.0601 ($[M - 3 ClO_4 - H_2O]^+$), $C_{68}H_{60}Cl_4Fe_3N_4O_{17}^+$; calc. 1512.0570).

Iron Complex $Fe_3(\mu_3-O)(4eH)_4(H_2O)(ClO_4)_3 \cdot 3 MeOH$ (3e**).** A soln. of **4e** (40 mg, 98 μ mol) and LiOH (5 mg, 208 μ mol) in MeOH (1 ml) and $CHCl_3$ (2 ml) was stirred at r.t. for 20 min. Then was added a soln. of $Fe(ClO_4)_3 \cdot x H_2O$ (45 mg, 127 μ mol) in MeOH (0.5 ml), and the mixture was stirred at r.t. for 5 min. Slow evaporation of the solvent over 18 h gave **3e** (29 mg, 13 μ mol, 52% based on **4e**). Red solid. M.p. 218° (dec.). UV/VIS (H_2O): 271 (4.76). IR (ATR): 3291, 2976, 1727, 1626, 1593, 1487, 1441, 1403, 1359, 1315, 1214, 1167, 1092, 1068, 1010, 980, 875, 843, 806, 734, 654, 619, 572. ESI-MS: 1827.9 ($[C_{72}H_{68}Br_4Fe_3N_4O_{22}]^+$), 1809.9 ($[C_{72}H_{66}Br_4Fe_3N_4O_{21}]^+$), 1420.9 ($[C_{54}H_{50}Br_3Fe_3N_3O_{17}]^+$), 1402.9 ($[C_{54}H_{48}Br_3Fe_3N_3O_{16}]^+$), 905.05 ($[C_{72}H_{67}Br_4Fe_3N_4O_{21}]^{2+}$). HR-ESI-MS: 1805.9035 ($[M - 3 ClO_4 - H_2O]^+$), $C_{72}H_{68}Br_4Fe_3N_4O_{21}^+$; calc. 1809.8960).

Gif-Type Oxidation of α -Pinene (22**).** α -Pinene (**22**; 275 mg, 2.02 mmol) and the respective iron complex **3** (7 μ mol) were dissolved in pyridine (27 ml) and AcOH (2.3 ml). Zinc powder (1.31 g, 20.0 mmol) was added, and the mixture was stirred under O_2 (1 atm) at r.t. for 18 h. Then, an aliquot (5 ml) was taken, which was diluted with H_2O (5 ml) and extracted with Et_2O (3×10 ml). The combined org. layers were washed sequentially with H_2O (30 ml), 1N HCl (30 ml), and brine (30 ml), and then dried ($MgSO_4$). After filtration, the org. layer was analyzed by capillary GC. The product ratio was determined by addition of a defined amount of **23**. The retention times of α -pinene (**22**), myrtenol (**23**), verbenone (**24**), myrtenal (**25**), and α -pinene oxide (**26**) were compared with authentic reference samples. The reproducibility was checked by repeating each catalytic experiment three times.

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Received May 9, 2011