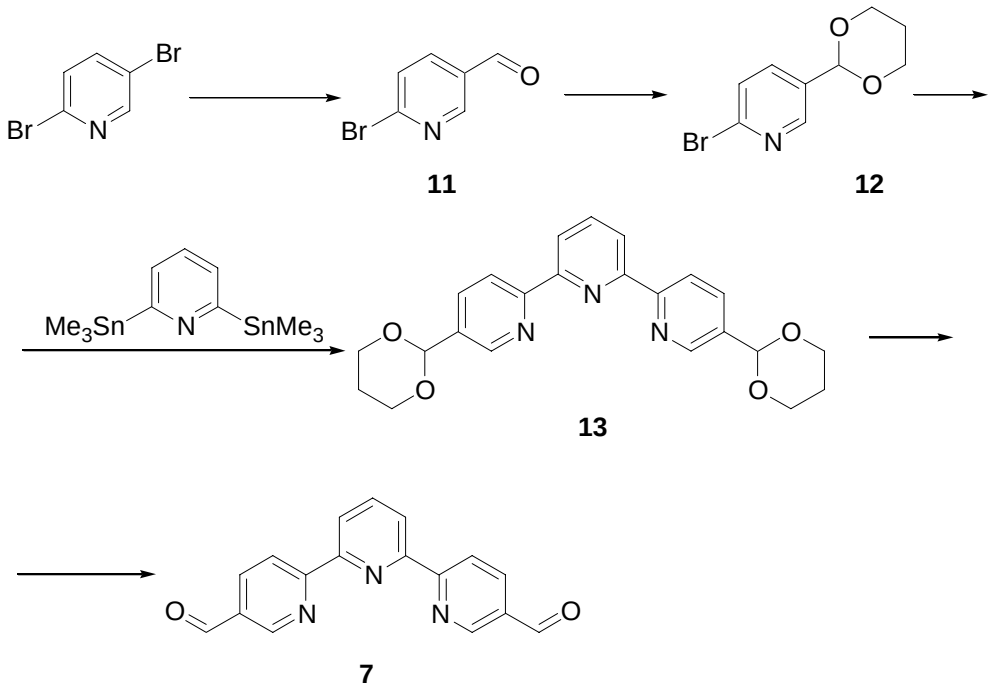
Supplementary material for Goral *et al*. (2001) *Proc. Natl. Acad. Sci. USA* **98** (4), 1347–1352. (10.1073/pnas.031579698)



Scheme 3. Synthesis of dialdehyde 7

2-Bromo-5-formylpyridine **(11):** To a slurry of 2,5-dibromopyridine (1.281 g, 5.4 mmol) in anhydrous ether (12 ml) cooled to –78°C in acetone/dry-ice bath, *n*-butyllithium (2.162 ml, 2.5 N in hexane) was added at such a rate that the temperature of reaction mixture did not exceed –60°C. After addition was complete, the reaction mixture was allowed to warm to –40°C over 30 min and kept at this temperature for 1.5 h, resulting in a brown--yellow slurry. The solution prepared in this manner was cooled to –78°C and used in the subsequent reaction.

N,*N*-dimethylformamide (0.46 ml) dissolved in 1 ml of ether was added within 20 min to a solution of 2-bromo-5-lithiopyridine at –78°C. The deep brick-red solution was stirred for 1 h at –78°C, then allowed to warm to –20°C and hydrolyzed with 3 ml of 6 N HCl. The aqueous phase was separated and extracted with ether 5 × 20 ml. Organic phases were combined and dried over $MgSO_4$. The product was recrystallized from ether as brown needle crystals. Yield 0.665 g, 79%. ^{1}H NMR (400 MHz, CDCl3): δ = 7.68 (d, $J_{H\text{-}3,H\text{-}4}$ = 8.057 Hz, 1H; H-2), 8.02 (dd, $J_{H\text{-}4',H\text{-}3'}$ = 8.057 Hz, , $J_{H\text{-}4,H\text{-}6}$ = 2.197 Hz, 1H; H-4), 8.823 (d, $J_{H\text{-}6',H\text{-}4'}$ = 2.197 Hz, 1H; H-6), 10.08 (s, CHO). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 129.2, 137.7, 152.7, 189.7 – CH, 148.5, 199.7 – C. FAB MS: *m*/*z*, M + 1 = 186.01, M + 3 = 187.4.

Protected aldehyde **12**: To a solution of 2-bromo-5-formylpyridine (0.754 g, 4.83 mmol in 15 ml of anhydrous benzene) propanediol (1.5 ml, 19 mmol) and PPTS ($C_5H_5N^+HtsO^-$) (0.15 g, 0.6 mmol) was added and mixture was refluxed with water separation for 1.5 h. The solvent was evaporated *in vacuo*, and reaction mixture was dissolved in ether, washed with $NaHCO_3$ solution and brain, and dried over $MgSO_4$. Product was recrystallized from ether to yield 0.947 g, 80.4% of yellow crystals. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (d, $J_{H\text{-}3,H\text{-}4}$ = 8.241 Hz, 1H; H-3), 7.66 (dd, $J_{H\text{-}4,H\text{-}3}$ = 8.241 Hz, $J_{H\text{-}4,H\text{-}6}$ = 2.197 Hz, 1H; H-4), 8.44 (d, $J_{H\text{-}6,H\text{-}4}$ = 2.197 Hz, 1H; H-6). ^{13}C NMR (125 MHz, $CDCl_3$):δ = 25.7, 67.5, CH_2; 99.1, 127.8, 136.7,148.6 – CH, 183.1 – C. FAB MS: *m*/*z*, M + 1 = 243.9, M + 3 = 245.9.

5,5″-(1,3-Dioxane)-2,2′: 6′2″-terpyridine **(13):** Compound **12** (0.971 g, 3.98 mmol) and 2,6-bis(trimethylstanyl)pyridine (0.679 g, 1.68 mmol) were dissolved in anhydrous toluene (25 ml). The solution was degassed twice. Then $(Ph_3P)_4Pd$ (0.076 g, 0.06 mmol) was added, and the mixture was degassed again. After the mixture was heated under reflux for 60 h in a dark place, a saturated solution of KF (10 ml) was added and the precipitate removed by filtration and washed with toluene. The organic phase was separated and the aqueous layer was extracted with toluene (3 × 20 ml). The organic phases were combined and dried over $MgSO_4$. Toluene was evaporated and product redissolved in minimum amount $CHCl_3$. This solution was poured in ethyl acetate. Product was precipitated, filtrated, and washed with cooled ethyl acetate. Yield 0.29 g, 59%. ^{1}H NMR (300 MHz, CDCl3): δ = 7.96 (dd, $J_{H\text{-}4,H\text{-}6}$ = 2.197 Hz, $J_{H\text{-}4,H\text{-}3}$ = 8.24 Hz, 2H; H-4), 7.935 (t, $J_{H\text{-}4',H\text{-}3'}$ = 7.69 Hz, 1H; H-4′), 8.447 (d, $J_{H\text{-}3',H\text{-}4'}$ = 7.69 Hz, 2H; H-3′), 8.598 (d, $J_{H\text{-}3,H\text{-}4}$ = 8.24 Hz, 2H; H-3), 8.765 (d, $J_{H\text{-}6,H\text{-}4}$ = 2.197 Hz, 2H; H-6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.25, 25.67, 65.83, 67.38, 97.76, 120.62, 121.25, 134.17, 134.59, 137.82, 147.34. FAB MS: *m*/*z*, M + 1= 406.0.

5,5′-Carbaldehyde-2,2′:6′,2”-terpyridine **(7): 13** (0.29 g, 1 mmol) was dissolved in 30 ml of $CHCl_3$, and 30 ml of 6N HCl was added. The reaction mixture was stirred overnight at room temperature. The aqueous layer was separated, made alkaline with Na_2CO_3, and extracted with $CHCl_3$ (5 × 30 ml). The organic phase was dried over $MgSO_4$, and evaporated to give **7** as a white solid. Yield 0.27 g, 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (t, $J_{H\text{-}4',H\text{-}3'}$ = 8.06 Hz, 1H; H-4′), 8.35 (dd, $J_{H\text{-}4,H\text{-}3}$ = 8.06 Hz, $J_{H\text{-}4,H\text{-}6}$ = 2.2 Hz 2H; H-4), 8.64 (d, $J_{H\text{-}3',H\text{-}4'}$ = 8.06 Hz, 2H; H-3′), 8.81 (d, $J_{H\text{-}3,H\text{-}4}$ = 8.06 Hz, 2H; H-3), 9.16 (d, $J_{H\text{-}6,H\text{-}4}$ = 2.2 Hz, 2H; H-6), 10.2 (s, CHO). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 121.3, 123.2, 131.3, 136.8, 138.4, 151.8, 154.3, 160.3, 190.5 FAB MS: *m*/*z*, M + 1 = 290.1.

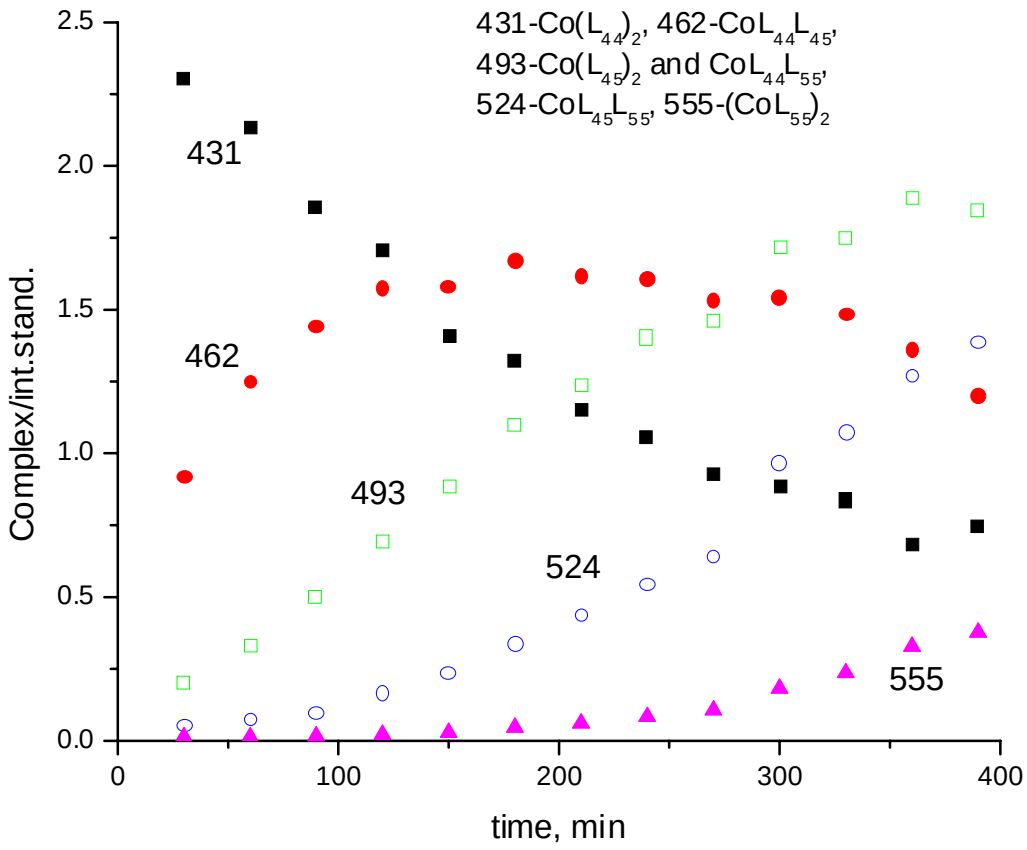


Fig. 6. Kinetics of the imine exchange in acyl hydrazone complexes.

Hydrozide exchange was performed with Co(II) complex (benzoyl hydrozide and acetyl-Co($\mathbf{L_{44}}$)$_2$-complex).

Reaction Conditions
pH 3.0
t′C 60
0.01M NH_4OAc Buffer Solution
[Co($\mathbf{L_{44}}$)$_2$]Cl_2 = 3 x 10^{-4} M
[Benzoyl hydrozide] = 6 x 10^{-3} M

Samples were collected every 30 min.

LC/MS conditions:
Total volume – 609.7 µl
29 µl I.S., 97.7 µl sample, 483 µl of 30 MeCN in pH 3.0 ammonium acetate buffer (final concentration 0.01 M)
Internal standard (IS) *m/z* 228
[IS] = 1.1 e^{-6} M
[Co($\mathbf{L_{44}}$)] = 4.8 e^{-5} M
[Benzoyl hydrazine] = 9.6 e^{-4} M
LC/MS method (“LCMS 3×”), 10-µl injections, 5 postflushes (autosampler), 70% buffer, 30% MeCN, 200 µl/min

Formation of a sample library of oxime ethers

Aldehyde **7** (0.02 g, 0.07 mmol) was dissolved in 10 ml of $MeNO_2$. To this solution, a mixture of methylhydroxylamine hydrochloride (0.017 g, 0.2 mmol), ethylhydroxylamine hydrochloride (0.02 g, 0.2 mmol), and benzylhydroylamine hydrochloride (0.029 g, 0.2 mmol) in 15 ml of nitromethane was added. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated, and the solid was redissolved in 5 ml of MeOH. To this solution, 585 μl of 0.06 N $CoCl_2$ solution in water was added. MS analysis showed the entire spectrum of all possible complexes, as shown in Fig. 7.

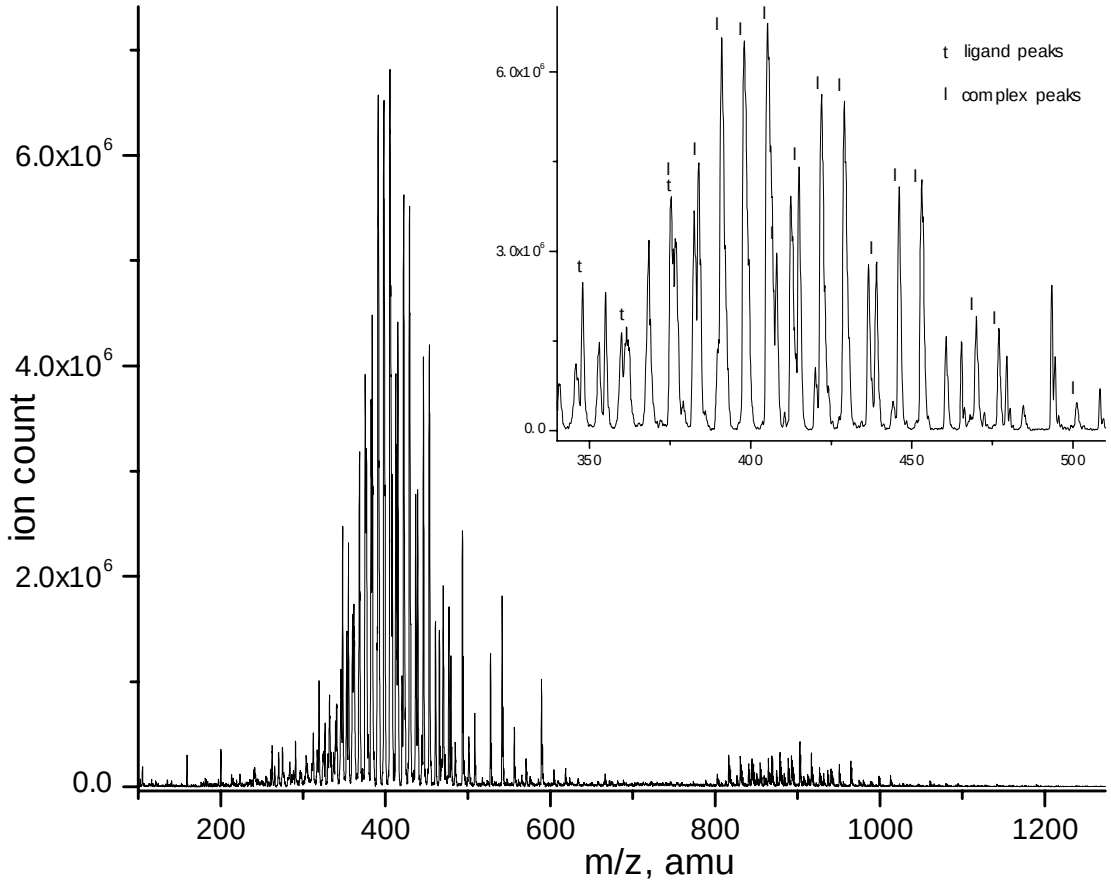


Fig. 7. Electrospray ionization MS spectrum of the library consisting of Co(**10**)$_2^{2+}$ complexes with R_1, R_2 = OMe, OEt, OBn (see Scheme 2). (*Inset*) Expanded region with labeled molecular peaks of the doubly charged library components.