Synthesis and Characterization of a New Tetradentate Ligand for Cu(II) Metal Ions

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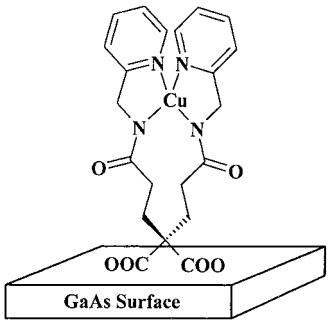
Received June 27, 2001

The synthesis and characterization of a tailor-made ligand **1** is described. Self-assembly of **1** on a GaAs surface was studied by FT-IR spectroscopy. The IR spectrum of the thin film points to the conclusion that the monolayer adsorbs to the surface via both carboxylates of the malonic acid derivative. The distinction between the possible binding modes is discussed.

The use of organic molecules as receptors for metal ions is well established.[1] The majority of the reports describe solution-state chelation of metal ions by various organic ligands. Apart from high ligand−analyte affinities, chelation by a monolayer adsorbed on solid support demands more complex prerequisites to succeed. These include higher sensitivities, as concentration of adsorbed ligands is small, and structural constraints that arise from the contribution of surface interactions.[1,2] Given the vast spectrum of technological applications such as catalysis, lithography, and molecular recognition, the interest in chemistry and physics underlying these applications has been on the rise in recent years.

Our synthetic aim was to prepare bifunctional ligand molecules that contain receptor sites capable of binding copper(II) metal ions and anchor moieties that can specifically bind to the gallium arsenide (GaAs) surface. Of the three structural features that make up a ligand suitable for adsorption as an organic thin film, e.g., receptor, spacer, and anchor, it is the receptor site that should be fitted to bind strongly and selectively to the analyte. The spacer essentially acts to assist in securing a stronger unhindered binding away from the surface while the anchor allows strong and irreversible binding to the solid surface. It has previously been demonstrated that binding to GaAs can be achieved via thiols,[2] disulfides,[2] phosphates,[3] or carboxyl groups.[2] Disulfides were found to bind relatively weakly to the GaAs surface, while the phosphates and carboxylates are stronger binders. The advantage of binding the ligand via a two-site dicarboxylate lies in the greater strength of the bonding as compared with sulfides or monocarboxylates.[4]

Previously synthesized dicarboxylic ligands have utilized the labile tartaric acid moiety. Due to the difficulties of the group in surviving multistep synthetic manipulations, a protected malonate was used in the synthesis of **1**. The synthesis of the suitable ligand was envisioned to begin at the anchor, utilizing suitably protected malonic acid as shown in Scheme 1.



1

The tetradentate receptor site with the amide and pyridyl donors as constructed for ligand **1**, though previously determined to have a binding constant of only 3.41, was found to be suitable for strainless binding of the Cu(II) ion.[5] The higher stability of the copper complex as compared to the stabilities of the other metal ion complexes utilizing the same ligand was evident.[5] It is in full agreement with the larger flexibility of the copper ion center toward tetrahedral distortions.

The synthesis of the ligand's backbone started, according to our preferred pathway, with the alkylation of *tert*-butyl malonate[6] **2**. Condensation of **2** with methyl 3-bromopropionate[7] gave **3** as a slowly crystallizing solid. Compound **3** consists of both the binding groups (the protected 1,3-dicarboxylic acid) that are later transformed to adsorb to the GaAs surface and the alkyl ester spacers to which the receptor center is to be attached. Basic saponification of the methyl esters in **3** gave the desired diacid **4** in 58% yield (over two steps). Carbodiimide-catalyzed coupling of the diacid with 2-picolylamine

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(1) (a) Göpel, W., Hesse, J., Zemel J. N., Eds. *Sensors: Chemical and Biochemical Sensors*; VCH Publishers: Weinheim, 1991−1992; Vols. 2 and 3. (b) Prodi, L.; Bolletta, F.; Zaccheroni, N.; Watt, C. I. F.; Mooney, N. J. *Chem. Eur. J.* **1998**, *4*, 1090−1094. (c) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515−1566.

(2) (a) Vilan, A.: Ussyshkin, R.; Gartsman, K.; Cahen, D.; Naaman, R.; Shanzer, A. *J. Phys. Chem. B* **1998**, *102*, 207−209. (b) Bastide, S.; Butruille, R.; Cahen, D.; Dutta, A.; Libman, J.; Shanzer, A.; Sun, L.; Villan, A. *J. Phys. Chem. B* **1997**, *101*, 2678.

(3) Artzi, R. MSc. Dissertation, The Weizmann Institute of Science, December 1999.

(4) Vilan, A. MSc. Dissertation, The Weizmann Institute of Science, November 1996.

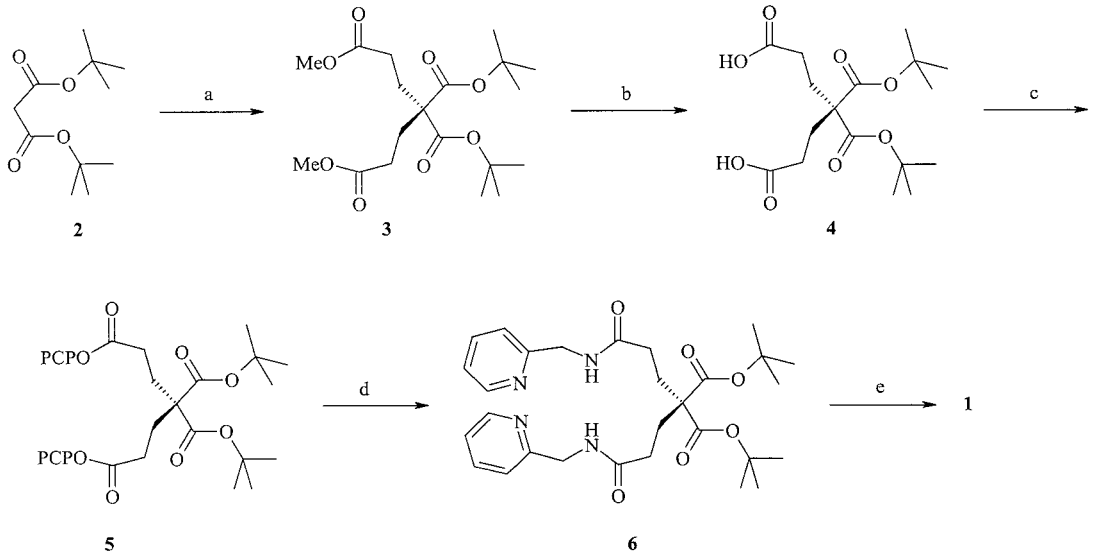
(5) Comba, P.; Goll, W.; Nuber, B.; Várnagy, K. Eur. *J. Inorg. Chem.* **1998**, 2041−2049.

(6) *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 263−266.

(7) Methyl acrylate may be used instead.

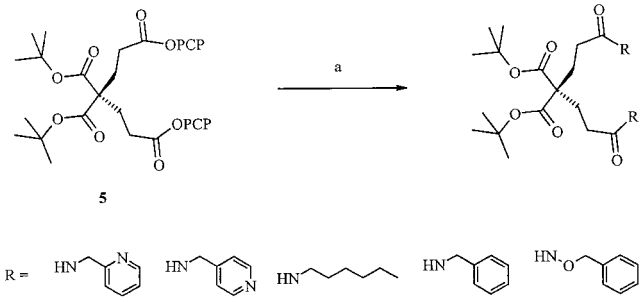
10.1021/jo010661u CCC: $22.00
Published on Web 05/14/2002

Scheme 1. BOC-malonate Pathway[a]



[a] Key: (a) methyl bromopropionate, NaH, THF, 5 h, rt, 89%; (b) NaOH, MeOH, 8 h, rt, 65%; (c) PCP−DCC complex, EtOAc, 3 h, rt, 83%; (d) 2-picolylamine, triethylamine, CH_2Cl_2, 8 h, rt, 92%; (e) TFA, CH_2Cl_2, 8 h, rt, 93%.

Scheme 2[a]



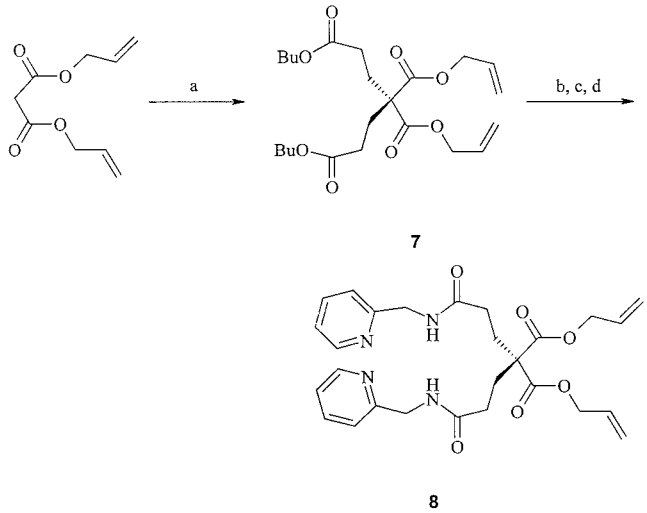
[a] Key: (a) amine of choice, triethylamine, CH_2Cl_2, 5−12 h, rt, 65−90% yield.

under DCC/HOBT conditions gave only low yields of the desired product **6** and a larger yield of an unidentified product, probably resulting from intramolecular DCC-mediated cyclization. Activation of the diacid toward amide formation was best achieved by the reaction of diacid **4** with a solid pentachlorophenol−dicyclohexylcarbodiimide complex (PCP−DCC complex).[8] Under these conditions, the organic acid is added to a suspension of excess complex in ethyl acetate and stirred for 3 h.

The active diester **5** was separated from the urea and pentachlorophenol side products as white solid in 83% yield. This reactive intermediate, prepared in gram quantities, is quite stable and could be stored with out degradation for extended periods of time. It has been used in our laboratory in the synthesis of various other ligands such as those shown in Scheme 2.[9]

Treatment of **5** with 2-picolylamine, in the presence of triethylamine, gave diamide **6** in a very good yield, i.e., 77% yield over two steps as compared with yields lower than 40% obtained for the direct conversion of **4** to **6**. Removal of the *tert*-butyl groups with trifluoroacetic acid in methylene chloride gave the desired ligand **1** as a viscous, colorless oil in nearly quantitative yield (41% yield over five steps).

Scheme 3. Alloc-malonate Pathway[a]



[a] Key: (a) *tert*-butyl bromoacetate, NaH, THF, 5 h, rt, 89%; (b) TFA, CH_2Cl_2, 5 h; (c) PCP−DCC complex, EtOAc, 3 h, rt; (d) 2-picolylamine, triethylamine, CH_2Cl_2, 8 h, rt, 75%.

Alternatively, we used diallyl malonate (Alloc ester) as the protected diacid for step 1 of the synthesis (Scheme 3). Alkylation with *tert*-butyl bromoacetate and deprotection of the resulting di-*tert*-butyl diester **7** with TFA gave the diacid **8** that was, similar to **4**, converted to the diamide compound via the PCP−DCC approach. Palladium-catalyzed removal of the Alloc groups in the presence of potassium ethyl hexanoate[10] afforded **1** in a low yield.

Attempts to grow and isolate a single crystal of the **1-Cu**$^{2+}$ complex were difficult as the formation of carboxylate−Cu^{2+} salts was interfering. To evade the carboxylate interferences in the binding and be able to study the complexation, we prepared the complex of **6**, where ligation occurs exclusively through the receptor site. Stable white powdery complex **6-Cu**$^{2+}$ was obtained upon stirring **6** in a two-phase water−methylene chloride

(8) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, 2nd ed.; Springer-Verlag: Berlin, 1994.

(9) Benshafrut, R. Unpublished results.

(10) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.

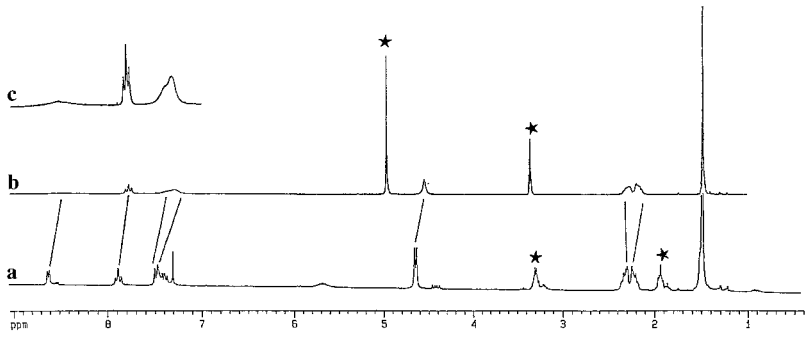


Figure 1. (a) ^{1}H NMR spectra of free **6**; (b) **6-Cu**$^{2+}$ complex; (c) enhancement (×6) of the aromatic region showing the broad peak at 8.52 ppm. Signals marked with an asterisk are due to MeOH and THF solvent impurities.

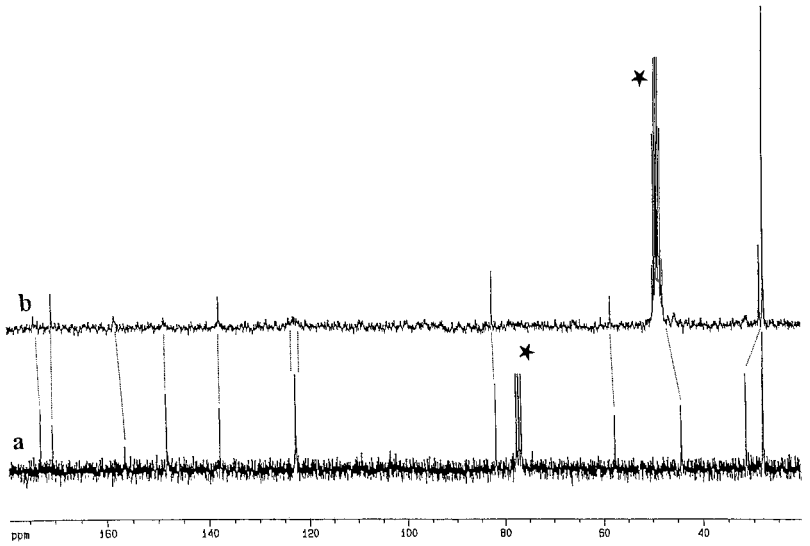


Figure 2. (a) ^{13}C NMR spectra of free **6** and (b) **6-Cu**$^{2+}$ complex. Signals marked with an asterisk are due to MeOH and $CHCl_3$ solvent impurities.

mixture containing $CuSO_4$. The ^{1}H NMR and ^{13}C NMR spectra of the complex, obtained after evaporation of the organic phase, provided direct evidence of the successful complexation at the receptor site (Figures 1 and 2).

The largest shift (downfield shift of $\Delta\delta = 1.5$ ppm) was observed in the ^{13}C NMR spectra for the α pyridyl carbon situated next to the chelating pyridyl-nitrogen atom. Smaller yet similar downfield shifts were observed for the remaining pyridyl carbons. While complexation with the paramagnetic ion did not result in any significant shifts, both the proton and carbon NMR signals for the atoms situated at or near the receptor site suffered from intensive broadening. The benzyl methylene protons, for example, that appeared as a doublet at 4.53 ppm in the ^{1}H NMR spectrum of free **6**, came into view as a broad singlet at 4.47 ppm in the spectrum of the copper complex. On the other hand, the terminal *tert*-butyl groups and the methylene groups exhibited no broadening, suggesting that they were unaffected by the formation of the complex. Furthermore, this supports the conclusion that this host−guest interaction at the internal receptor cavity of **6** closely resembles the host−guest interaction expected in **1**.

Self-assembly of **1** on 5 × 5 mm GaAs slides was achieved by immersing the slides for 12 h in a DMF solution having a concentration of 38 mM of the adsorbate **1**. Examination of the infrared spectra of the slides

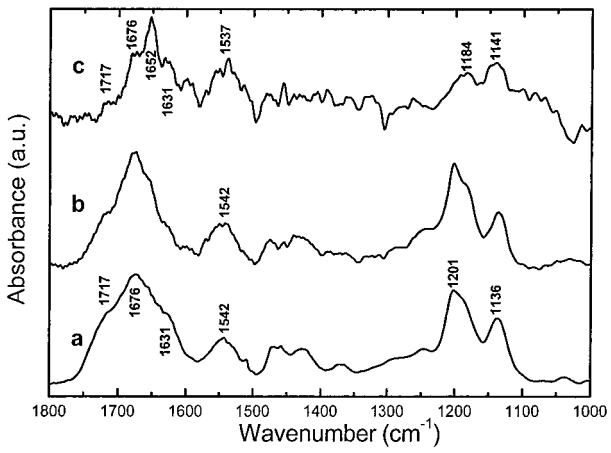
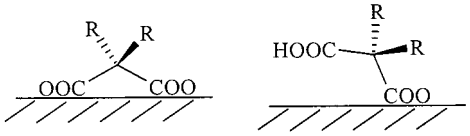


Figure 3. Infrared spectra of ligand **1**: (a) neat on a NaCl pellet, (b) excess ligand on a GaAs surface prior to washing, and (c) adsorbed ligand after washing in 1:1 hexane/2-propanol for 15 s. Only the 1800−1000 cm^{-1} region is shown. Note: the spectra of neat **1** and excess (a and b) are scaled down by 10 for clarity.

indicated that the monolayer of **1** was successfully formed (Figure 3).

In the process of adsorbing the ligand molecules onto the GaAs surface two basic modes of adsorption may be considered (shown below): mode 1 in which all of the adsorbate molecules bind through the carboxylic acid

groups and mode 2 in which the preferred adsorption is through a single carboxylic arm keeping the second arm unbound and away from the surface. It is, however, reasonable to assume that a mixture of the two modes could be present and that parameters such as adsorbate concentration, solvent interactions, intermolecular effects, and the distance of one carboxylic group from the surface relative to the other could favor the existence of one mode over the other.



Mode 1 Mode 2

Neat **1** exhibites an FT-IR spectrum consistent with internal hydrogen bonding. Apart from the C═O stretching corresponding to the carboxylic acids ($\nu_{C=O}$ = 1717 cm^{-1}), two other stretching frequencies contribute to the broadening of the peak between 1600 and 1750 cm^{-1}, i.e., amide C═O bands ($\nu_{C=O}$ = 1676 and 1631 cm^{-1}) and pyridine skeletal bands ($\nu_{C=N}$ = 1600 cm^{-1}). The position of the bands corresponding to the amide and pyridine groups in the IR spectrum of the adsorbed **1** should not change, as these groups do not participate in the adsorption to the GaAs surface. Quenching the hydrogen bonding effect in **1** by means of salt formation or by adsorption to the GaAs surface, according to mode 1, should result in the disappearance of the 1717 cm^{-1} shoulder and the emergence of a carboxylate band at $\nu_{C=O}$ = ~1650 cm^{-1}. However, if mode 2 is preferred, the interruption in the hydrogen bonding should give rise to a carboxylic acid band at a higher frequency, ~1750 cm^{-1},[11] and a carboxylate band at or around 1650 cm^{-1}.

After an adsorption process of 12 h and withdrawal of the slide from the solution, excess unbound ligand covers the bound monolayer. The characteristic infrared bands of this bulk are closely similar to the IR characteristics of the neat material (Figure 3a,b). The bound monolayer uncovered by rinsing the device in a 1:1 solution of hexane and 2-propanol exhibits carboxylate adsorptions that are indicative of mode 1. On binding to the surface (Figure 3c), a Ga-carboxylate species forms giving rise to the carboxylate bands at 1652 (strong and asymmetrical) and a weaker and symmetrical band at a lower frequency. A trace of excess adsorbate is seen in Figure 3c at 1717 cm^{-1}. The bands that should appear if mode 2 were to prevail are clearly absent.

No change was observed for the amide bands at 1676 and 1631 cm^{-1} and the pyridine rings at 1600 cm^{-1}. This indicates that there is no detectable effect on the receptor site that can arise either from some surface interaction or from complexation of contaminants that may be present on the GaAs surface or in the solution, prior to or during monolayer formation. Continuous rinsing of the GaAs slice with the organic solution mentioned above does not further affect the stability of the bound monolayer.

(11) (a) Meloan, C. F. *Elementary Infrared Spectroscopy*; Macmillan Publishers: New York, 1963. (b) Lambert, J. B.; Shurvell, H. F.; Lightner, D. A.; Cooks, R. G. *Introduction to Organic Spectroscopy*; Macmillan Publishers: New York, 1987.

Experimental Section

General Comments. All chemicals were analytical grade and were used without further purification. All glassware was washed with acetone and dried in an oven at 120 °C before use. ^{1}H NMR spectroscopy was performed on a 250 MHz spectrometer or on a 400 MHz spectrometer as indicated. All ^{13}C and ^{1}H NMR spectra were obtained in $CHCl_3$-*d*, except where noted. Column chromatography was performed with silica gel 60 (230−240 mesh). Melting points are uncorrected. All reactions were carried out in a nitrogen atmosphere. Standard workup means that the organic layers were pooled after extraction, washed with water, dried over $MgSO_4$, filtered, and evaporated under reduced pressure.

Ligand Adsorption. GaAs slides were immersed in a 38 mM DMF solution of the ligand for a period of 12 h, under an atmosphere of nitrogen. The slides were then taken out of the solution, rinsed with a 1:1 solution of hexane and 2-propanol, and dried with N_2.

Tetra Ester 3. A 13.06 g (60.4 mmol) portion of malonate **2** and 22.21 g (132.9 mmol, 2.2 equiv) methyl bromopropionate were introduced into a one-neck 200 mL round-bottom-flask containing 75 mL of THF. Into the well-stirred solution was added NaH (60% in oil) in small portions in such a way that the evolution of hydrogen gas ceases before the next portion is added. The solution was allowed to stir at room temperature for 5 h before it was quenched with water and extracted with ether (3 × 75 mL). Workup afforded nearly colorless oil that solidified slowly into a white mass. Recrystallization from methanol−hexane gave 20.97 g of the desired solid (89.5% yield). Mp: 66.5 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 1.46 (s, 18H), 2.15 (t, 4H), 2.35 (t, 4H), 3.79 (s, 6H). ^{13}C NMR (62 MHz, $CDCl_3$, δ): 25.9, 26.4, 27.6, 29.5, 51.3, 81.3, 169.8, 170.1. GC−MS (EI): 388 (M^+, 1), 277 (100). IR (CCl_4, NaCl): 2981, 1725, 1655, 1618, 1446, 1146 cm^{-1}.

Diacid 4. A 3.06 g (7.88 mmol) portion of **2** in 75 mL of methanol was treated with 5 mL of a 2 N NaOH solution. The solution was stirred overnight before its volume was reduced in half in vacuo. The thick solution was acidified to pH 5 with dilute HCl and extracted with chloroform (3 × 75 mL). Workup gave **4** as a white solid in 65.0% yield. Mp: 140.5 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 1.42 (s, 18H), 2.09 (t, 4H), 2.32 (t, 4H), 8.30 (br s, 2H). ^{13}C NMR (62 MHz, $CDCl_3$, δ): 26.4, 27.6, 28.9, 57.0, 81.8, 169.5, 178.3. MS (ESI-MS, *m*/*z*): 359 (M − H, 100). IR (CCl_4, NaCl): 3395, 3075, 1721, 1701, 1434, 1253, 1142 cm^{-1}.

Active Diester 5. A 50 mL portion of ethyl acetate and 7.00 g (6.96 mmol) of the PCP−DCC complex were introduced into a 100 mL flask. The nearly homogeneous solution was then treated with 1.0 g (2.77 mmol) of diacid **4** in 15 mL of ethyl acetate, added in one portion. Within 10 min of the addition, the solution was clear and the urea started to precipitate. The mixture was stirred at room temperature for an additional 3 h, after which time the urea was filtered off and the solvents were evaporated in vacuo to afford a thick mass. The residue was chromatographed twice on silica (eluted with 5:1 hexane/ethyl acetate) to yield 1.95 g of the active ester as a white solid in 82.8% yield. Mp: 165.4 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 1.53 (s, 18H), 2.35 (t, 4H), 2.79 (t, 4H). ^{13}C NMR (62 MHz, $CDCl_3$, δ): 27.8, 27.9, 28.9, 57.0, 82.5, 127.6, 131.6, 132.0, 143.9, 168.6, 169.4. MS (FAB−): 856, 264 (100). IR (CCl4, NaCl): 2982, 1784, 1718, 1265, 1152 cm^{-1}.

Diamide 6. A 15.0 mL portion of methylene chloride in a 50 mL round-bottom flask was treated with 0.240 g (2.22 mmol) of 2-picolylamine and 0.5 mL of triethylamine. The solution was stirred at room temperature for 10 min prior to the addition of 0.857 g (1.0 mmol) of the active ester **5** in 5 mL of methylene chloride. After the solution was stirred for 8 h, the solvents were evaporated and the residue was chromatographed on silica (9.5:0.5 CH_2Cl_2/MeOH). The protected ligand **6** was obtained as a white solid in 92.5% yield (0.50 g). Mp: 134.2 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 1.47 (s, 18H), 2.22 (m, 4H), 2.26 (m, 4H), 4.57 (d, 4H, J = 5.0 Hz), 4.95 (br t, 2H, NH), 7.28 (m, 4H), 7.72 (t, 2H), 8.54 (d, 2H, J = 4.25 Hz). ^{1}H NMR (250 MHz, D_2O, δ): 1.47 (s, 18H), 2.22 (m, 4H),

2.26 (m, 4H), 4.53 (d, 4H), 7.44 (m, 4H), 7.89 (t, 2H), 8.53 (d, 2H, J = 4.25 Hz). ^{13}C NMR (62 MHz, $CDCl_3$, δ): 27.8, 27.9, 31.3, 44.1, 57.5, 81.7, 122.5, 122.6, 137.7, 148.1, 156.3, 170.1, 172.5. MS (ESI+): 541 (M + 1), 563 (M + Na). IR (CCl_4): 3265, 2977, 1721, 1647, 1245, 1163 cm^{-1}.

Complex 6-Cu^{2+}. In a two-phase mixture made of 50 mL of a 0.1 M Tris buffer (pH 7.5) and 50 mL methylene chloride were dissolved 65 mg of $CuSO_4$ pentahydrate followed by 31 mg of ligand **6**. The two-phase mixture was stirred vigorously at room temperature for 10 min. The aqueous phase was then separated and the organic phase dried and evaporated to afford a white crystalline complex. ^{1}H NMR (400 MHz, MeOD-d_3, δ): 1.49 (s, 18H), 2.12 (m, 4H), 2.26 (m, 4H), 4.47 (s, 4H), 7.33 (br s, 2H), 7.40 (br s, 2H), 7.81 (t, 2H), 8.52 (br s, 2H). ^{13}C NMR (100 MHz, MeOD-d_3, δ): 28.1 (CH_3), 28.9 (CH_2), 31.7 (CH_2CON), 45.7 (CH_2-Py), 58.6 (quaternary C-malonate), 83.0 (quaternary *tert*-butyl), 123.0 (aryl H4), 123.9 (aryl H2), 138.8 (aryl H3), 149.6 (aryl H1), 159.3 (aryl ipso), 171.5 (CO *tert*-butyl), 175.1 (CON).

Alloc 7. Into a 50 mL round-bottom flask fitted with a nitrogen inlet were added 10 mL of THF, 1.00 g (5.4 mmol) of Alloc-malonate ester, and 2.21 g (11.3 mmol, 2.1 equiv) of *tert*-butyl bromoacetate. The solution was stirred under nitrogen while NaH (60% suspension) was added in small portions in such a way that hydrogen gas evolution ceased before the next portion was added. The thick gray solution was allowed to stir at room temperature for 5 h before it was quenched with water and brine (50%). The solution was extracted with ether (3 × 50 mL), dried over $MgSO_4$, and evaporated to yield light yellow oil. Chromatography on silica and elution with a 5:1 mixture of hexane/ethyl acetate afforded the product as a nearly colorless oil in 89% yield. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 3.32 (s, 4H), 4.67 (d, J = 5.8 Hz), 5.30 (dd, 4H), 5.86 (m, 2H), 10.12 (br s, 2H). ^{13}C NMR (62 MHz, $CDCl_3$, δ): 36.9, 53.1, 66.9, 119.0, 131.0, 168.3, 176.4. IR (neat oil, NaCl): 3228, 2951, 2664, 1743, 1714, 1411, 1262 cm^{-1}.

Alloc 8. A solution of the activated Alloc-malonate ester in 10 mL of chloroform was added in one portion to a stirring solution of 0.250 g (2.31 mmol, 4 equiv) of 2-picolylamine and 350 μL of triethylamine in 15 mL of chloroform under a nitrogen atmosphere. The yellow solution was stirred at room temperature for 5 h and then evaporated under vacuo to yield a gray wet solid. The solid was chromatographed on silica eluted with a 9.5:0.5 mixture of CH_2Cl_2 and methanol (TLC ~ R_f = 0.5) to give 0.48 g of the product, 65% yield. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 3.0 (s, 4H), 4.65 (m, 8H), 5.25 (dd, 4H), 5.90 (m, 2H), 7.26 (m, 6H), 7.71 (t, 2H), 8.52 (d, 2H). ^{13}C NMR (62 MHz, $CDCl_3$, δ): 38.7, 43.4, 54.2, 65.8, 117.7, 122.1, 122.2, 131.4, 137.0, 147.6, 157.5, 168.9, 169.9. MS (FAB+): 481 (MH^+, 100), 423 (34), 373 (35.7).

Ligand 1. Deprotection of BOC Ester. A 0.210 g (0.41 mmol) portion of **6** was added to a 1:1 mixture of TFA and CH_2Cl_2 (3 mL) in a 25 mL round-bottom flask, under an atmosphere of nitrogen. The solution was stirred overnight, reduced in volume in vacuo, and washed four times with methylene chloride (5 mL). The viscous colorless oil amounted to 0.150 g, 92.5% yield.

Deprotection of Alloc Ester. A premade solution of 2 mL of ethylhexanoic acid in 5 mL of THF was treated with small pieces of potassium metal (10% excess) and was stirred until all the metal was consumed. Then, the solvent was removed under vacuum and the residue was dissolved in 5 mL of methylene chloride. In a separate 100 mL round-bottom flask, maintained under an inert atmosphere, were dissolved 0.20 g of Alloc **8**, 20 mg of triphenylphosphine, and 50 mg of tetrakis-(triphenylphosphine)palladium(0) in 70 mL of methylene chloride. The mixture was allowed to stir for 5 min before the hexanoate solution prepared separately was added in one portion. After 12 h, the dark solution was treated with 50 mL of ether. The oil, which separated, was acidified, extracted into CH_2Cl_2, and dried over $MgSO_4$. Evaporation of the dried organic solvent gave light brown oil that was identical with the product obtained from the BOC pathway. ^{1}H NMR (250 MHz, MeOD-d_3, δ): 1.72 (t, 4H), 1.94 (t, 4H), 4.26 (s, 4H), 7.50 (m, 4H0, 8.09 (t, 2H), 8.30 (d, 2H, J = 4.0 Hz). ^{1}H NMR (250 MHz, DMSO-d_6, δ): 2.20 (m, 4H), 2.13 (m, 4H), 4.51 (d, 4H, J = 5.45 Hz), 7.72 (m, 4H), 8.29 (t, 2H), 8.69 (m, 4H, aryl H's + amide H's). ^{13}C NMR (62 MHz, MeOD-d_3, δ): 29.2, 31.4, 41.8, 57.1, 126.5, 126.7, 142.3, 147.7, 155.5, 174.1, 175.9. MS (FAB−): 427 (M − H), 266 (100). HRMS (FAB+): found 429.1764, calcd for $C_{21}H_{25}N_4O_6$ 429.1774. IR (neat oil, NaCl): 3403, 3070, 2943, 1708, 1672, 1202, 1134 cm^{-1}.

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