Fe_3O_4 Nanoparticle-Supported Copper (I) Pybox Catalyst: Magnetically Recoverable Catalyst for Enantioselective Direct-Addition of Terminal Alkynes to Imines

Tieqiang Zeng,[a,b] Luo Yang,[b] Reuben Hudson,[b] Gonghua Song,[*a] Audrey R. Moores[b] and Chao-Jun Li*[b]

[a] *Shanghai Key Laboratory of Chemical Biology, Institute of Pesticides and Pharmaceuticals, East China University of Science and Technology, Shanghai 200237, P.R. China* ghsong@ecust.edu.cn

[b] *Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, Quebec, Canada, H3A 2K6* cj.li@mcgill.ca

Supporting information

General information:

All solvents and reagents were purchased from Aldrich chemical company and were used without prior purification. ^{1}H NMR spectra were recorded on Varian 300 and Varian 400 MHz spectrometer in $CDCl_3$ solution and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm). ^{13}C NMR spectra were obtained at 75 and 100 MHz. HRMS were made by McGill University. Flash column chromatography was performed over SORBENT silica gel 30-60 μm. Thin layer chromatography was performed using Sorbent Silica Gel 60 F_{254} TLC plates and visualized with ultraviolet light. Enantiomeric excess was determined with HPLC by using a chiralcel OD column and 1/20 hexane/ isopropanol as eluent

General procedure:

Dimethyl 4-hydroxypyridine-2,6-dicarboxylate[1]

Chelidamic acid hydrate (732 mg, 4 mmol) was suspended in methanol (20 mL) and sulfuric acid (97%) was carefully added at room temperature with vigorous stirring. The yellow solution was refluxed for 2 h and the solvents evaporated. Water (10 mL) was then added and the solution was neutralized with a saturated solution of $NaHCO_3$ to pH 8 and the aqueous solution was extracted with CH_2Cl_2 (4×20 mL). The organic phase was dried with Na_2SO_4 and evaporated to give product as a white solid (0.8 g, 95%). ^{1}H NMR (400MHz, [D_6] DMSO) δ 11.59 (s, 1H), 7.56 (s, 2 H), 3.86 (s, 6H); ^{13}C NMR (100MHz, [D_6]DMSO) δ 166.3, 165.2, 149.7, 115.7, 53.0; HRMS calcd. for $C_9H_{10}NO_5$ $[M+1]^+$: 212.0554, found 212.0552.

4-Bromopyridine-2,6-dicarboxylic acid dimethyl ester (3)[2]

Dimethyl 4-hydroxypyridine-2,6-dicarboxylate (0.8 g, 3.8 mmol) and phosphorus tribromide (5.5 mmol) were heated in $CHCl_3$ (15 mL) for 3 h at 90 °C. The dark solution was cooled to -30 °C and MeOH (25 mL) was added dropwise. The precipitated solid was filtered off and recrystallized from MeOH to afford 0.942 g of

the product as a white solid; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.45 (s, 2H), 4.03 (s, 6H).

4-Bromopyridine-2,6-dicarboxylic acid bis[((*S*)-2-hydroxy-1-phenylethyl)amide] (4)

A mixture of **3** (0.649 g, 2.37 mmol) and (*S*)-phenylglycinol (0.813 g, 5.93 mmol) was stirred in methanol (5 mL) at 115 °C for 5 h. The solution was concentrated in vacuo and the residue was purified by column chromatography (SiO_2, Dichloromethane/methanol 40:1) to yield the white solid product 1.033 g (90%). $[\alpha]_D^{20}$ -38.8 (*c* 0.015, CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.55 (d, *J* = 10, 2H), 8.43 (s, 2H), 7.32 (m, 10H), 5.23 (m, 2H), 3.99 (d, *J* = 5.0 Hz, 4H), 2.76 (br s, 2H).

4-Bromo-2,6-bis[(*S*)-4-phenyloxazolin-2-yl]pyridine (1)

A solution of **4** (1.079 g, 2.23 mmol), TsCl (1.058 g, 5.60 mmol), DMAP (24.2 mg, 0.2 mmol) and Et_3N (2 mL) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 3 h and then refluxed for 48 h. The mixture was washed with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic solutions dried (Na_2SO_4). After evaporation, the crude product was purified by column chromatography (SiO_2, Dichloromethane/methanol 200:1) to yield the white solid **1** (850 mg, yield: 85%). $[\alpha]_D^{20}$ -68.5 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.53 (s, 2H), 7.36 (m, 10H), 5.46 (dd, *J* = 8.8 and 8.8 Hz, 2H), 4.93 (dd, *J* = 8.8 and 10.4 Hz, 2H), 4.44 (t, *J* = 8.8 Hz, 2H).

SiO_2@Fe_3O_4 nanoparticles (5)[3]

Magnetite (Fe_3O_4) NPs (<50 nm particle size) were purchased from Sigma-Aldrich. Polyoxyethylene(5) nonylphenyl ether (10 mL, 21.8 mmol, Igepal CO-520, containing 50 mol % hydrophilic group, Aldrich) was dispersed in a round bottom flask containing cyclohexane (200 mL) by sonication. Next, 40 mg of Fe_3O_4 nanoparticles dispersed in cyclohexane were added to the reaction solution. The resulting mixture was mechanical stirred for 4 h. Then, an ammonium hydroxide solution (30%, 1.5 mL) was added to the reaction mixture. Lastly, tetraethylorthosilicate (4 mL, TEOS) was added, and stirred for 12 hr. The resulting silica nanospheres containing Fe_3O_4 nanocores were collected by magnetic decantation. The collected nanospheres were redispersed in EtOH and recovered by using a magnet. The dispersion of the nanosphere into EtOH suspension and magnetic separation was repeated three times for the purification.

SiO_2@Fe_3O_4 nanoparticles functionalized with amine groups (6)

3-Aminopropyltriethoxy-silane (5 mL) was added to the 100 mL of toluene suspension containing silica nanospheres containing Fe_3O_4 nanocores (325 mg) and stirred for 12 h at room temperature. The resulting silica nanospheres functionalized with amine groups were collected by magnetic decantation. The collected nanospheres (389 mg) were purified by repeating the re-dispersion into EtOH and magnetic separation.

SiO_2@Fe_3O_4 nanoparticles supported pybox (7)[4]

A flask was charged with CuBr (2.8 mg, 0.02 mmol), BINOL (5.7 mg, 0.02 mmol), K_3PO_4 (42.4 mg, 0.2 mmol), 4-bromopyridine-2,6-dicarboxylic acid bis[((*S*)-2-hydroxy-1-phenylethyl)amide] **(4)** (0.24 mmol) and **(6)** (0.2 mmol). The flask was evacuated and backfilled with argon (this procedure was repeated three times), and DMF (1 mL) were added to the flask under argon atmosphere. The flask was sealed and the mixture was allowed to stir under argon atmosphere at 50℃ for 12 h. After completion of the reaction, the nanospheres were collected by magnetic decantation. The collected nanospheres were purified by repeating the re-dispersion into EtOH and magnetic separation, washing with CH_2Cl_2 and aqueous EDTA solution for three times to eliminate cupper residue.

Fe_3O_4 nanoparticle-supported copper (I) pybox catalyst (8)

(7) (0.2 mmol, 470 mg) was stirred with a dichloromethane solution of $(CuOTf)_2$·toluene (0.2 mmol), filtered, and washed with CH_2Cl_2 and EtOH, yielding the magnetically recoverable Fe_3O_4 nanoparticle-supported copper (I) pybox (**8**).

The enantioselective addition of phenylacetylene to imines catalyzed by Fe_3O_4 nanoparticle-supported copper (I) pybox complex[5]

The mixture of aldehyde (0.2 mmol) and aniline (0.24 mmol) was heated at 60 °C for about two hours. Then pybox Fe_3O_4 nanoparticle-supported copper (I) complex (10 mol %, 0.02 mmol, 0.1 g), phenylacetylene (0.3 mmol) and CH_2Cl_2 (0.5 mL) were added into the mixture under argon. The mixture was stirred at 35 °C for 1.5-2 days. When the magnetic stirring was stopped, the magnetic Fe_3O_4 nanoparticle-supported copper (I) pybox complex was adsorbed on the magnetic stirring bar. The reaction solution was filtered through silica directly and washed with methylene chloride. After flash column chromatography on silica gel with 1/40 EtOAc/hexane as eluent, the product was isolated as a yellowish oil, which was purified further by recrystallization from methylene chloride/hexane to give pale yellow primes. The enantiomeric excess was determined by HPLC with a chiralcel OD column using hexane/ isopropanol (1:20) as eluent. The catalyst was washed with dichloromethane, dried under vacuum, and used directly for the next round of reaction without further purification.

The racemic product of addition of phenylacetylene to imines

The mixture of aldehyde (0.2 mmol) and aniline (0.24 mmol) was heated at 60 °C for about two hours. Then racemic phenyl-pybox (10 mol %), copper (I) triflate toluene complex (10 mol %), phenylacetylene (0.3 mmol) and CH_2Cl_2 (0.5 mL) were added into the mixture under argon. The mixture was stirred at 35 °C for 2 days. The reaction mixture was filtered through silica directly and washed with methylene chloride. After flash column chromatography on silica gel with 1/40 EtOAc/hexane as eluent, the product was isolated as a yellowish oil, which was purified further by recrystallization from methylene chloride/hexane to give pale yellow primes. The enantiomeric excess was determined by HPLC with a chiralcel OD column using

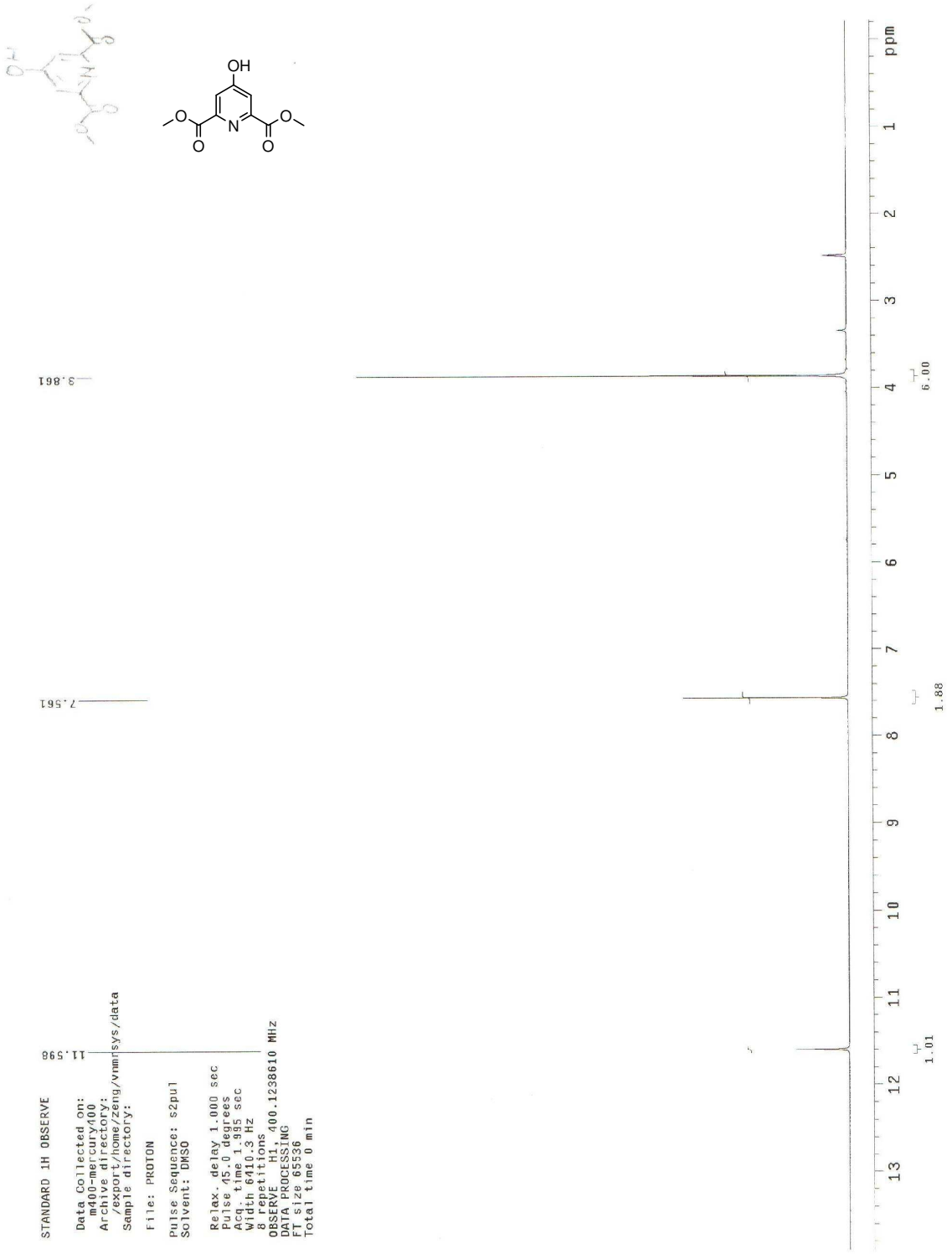
hexane/ isopropanol (1:20) as eluent.

***rac*-N-(1-Phenyl-3-p-tolyl-2-propynyl)-aniline.** HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 95:5, flow rate = 0.5 mL/min) t_R = 16.6 min, t_R = 19.0 min, Ee = 0%; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.68(d, *J*=7.6 Hz, 2H), 7.44-7.41(m, 2H), 7.38-7.32(m, 3H), 7.26-7.21(m, 2H), 7.11(d, *J*=7.6 Hz, 2H), 6.83-6.79(m, 3H), 5.51(s, 1H), 4.18(s, 1H), 2.35(s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 146.6, 139.9, 138.4, 131.7, 129.2, 129.0, 128.8, 128.1, 127.3, 119.7, 118.5, 114.1, 87.8, 85.2, 50.7, 21.5; HRMS (ESI) m/z: $[M+1]^+$ calcd for $C_{22}H_{20}N$, 298.1590; found: 298.1589.

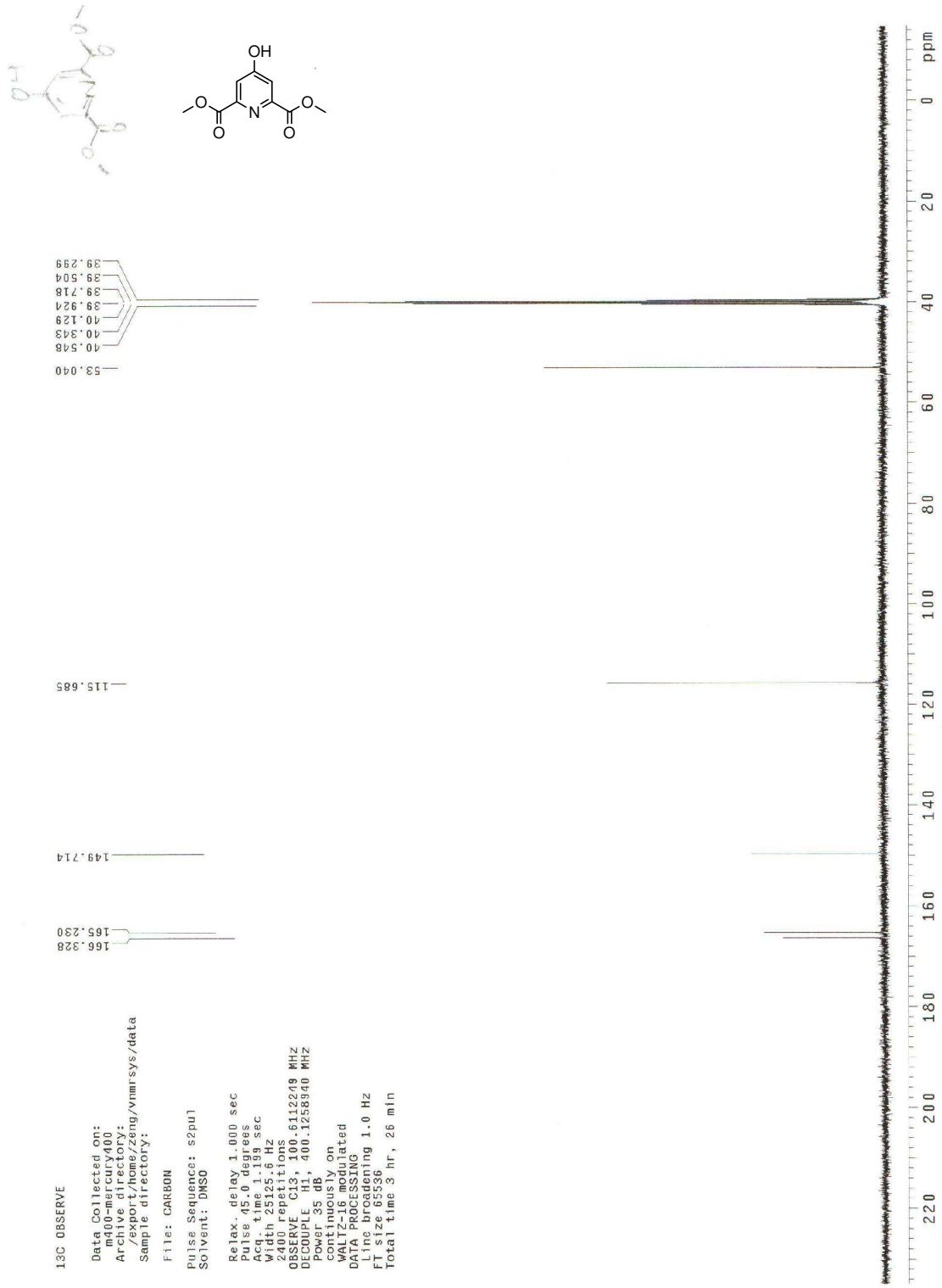
1. Chauvin, A.-S.; Comby, S.; Song, B.; Vandevyver, C. D. B.; Bünzli, J.-C. G. *Chem. Eur. J.* **2008**, *14*, 1726-1739.
2. Lundgren, S.; Lutsenko, S.; J□nsson, C.; Moberg, C. *Org. Lett.* **2003**, *5*, 3663-3665.
3. Choi, J; Kim, J. C.; Lee, Y. B.; Kim, I. S.; Parka, Y. K.; Hur, N. H. *Chem. Commun.* **2007**, 1644-1646.
4. Jiang, D. Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672-674.
5. Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638-5639.

NMR Spectra

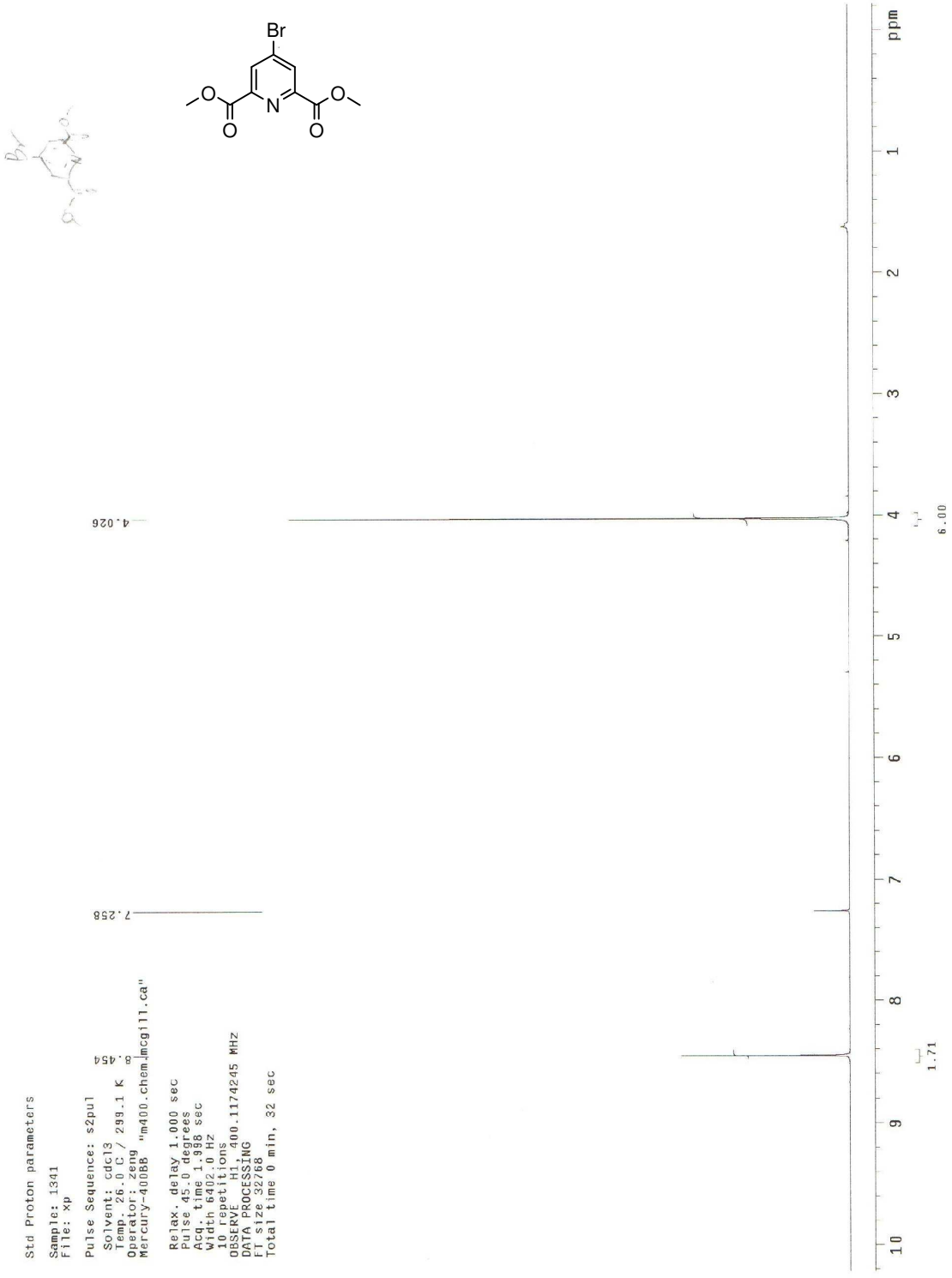
Dimethyl 4-hydroxypyridine-2,6-dicarboxylate



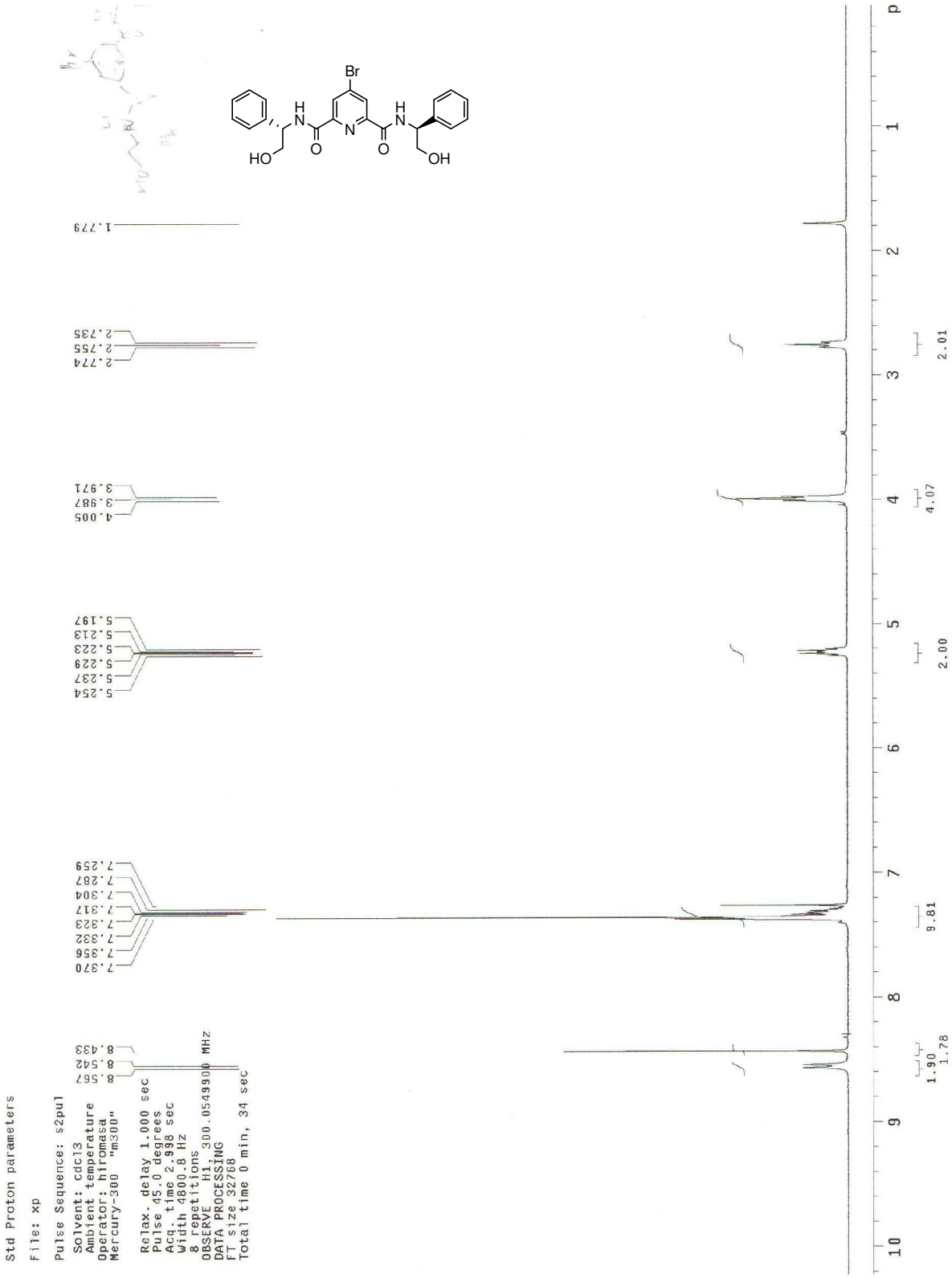
Dimethyl 4-hydroxypyridine-2,6-dicarboxylate



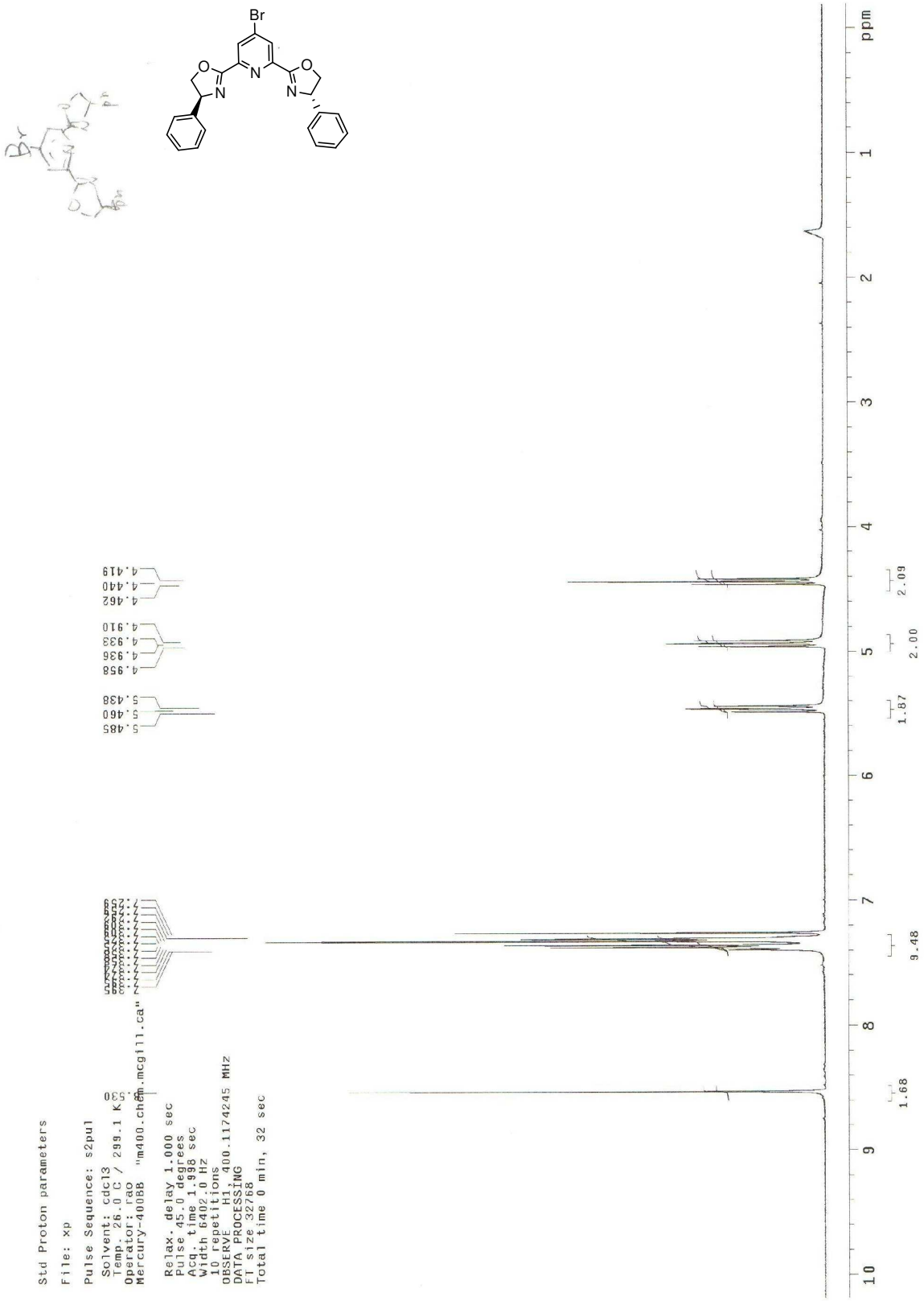
4-Bromopyridine-2,6-dicarboxylic acid dimethyl ester **(3)**



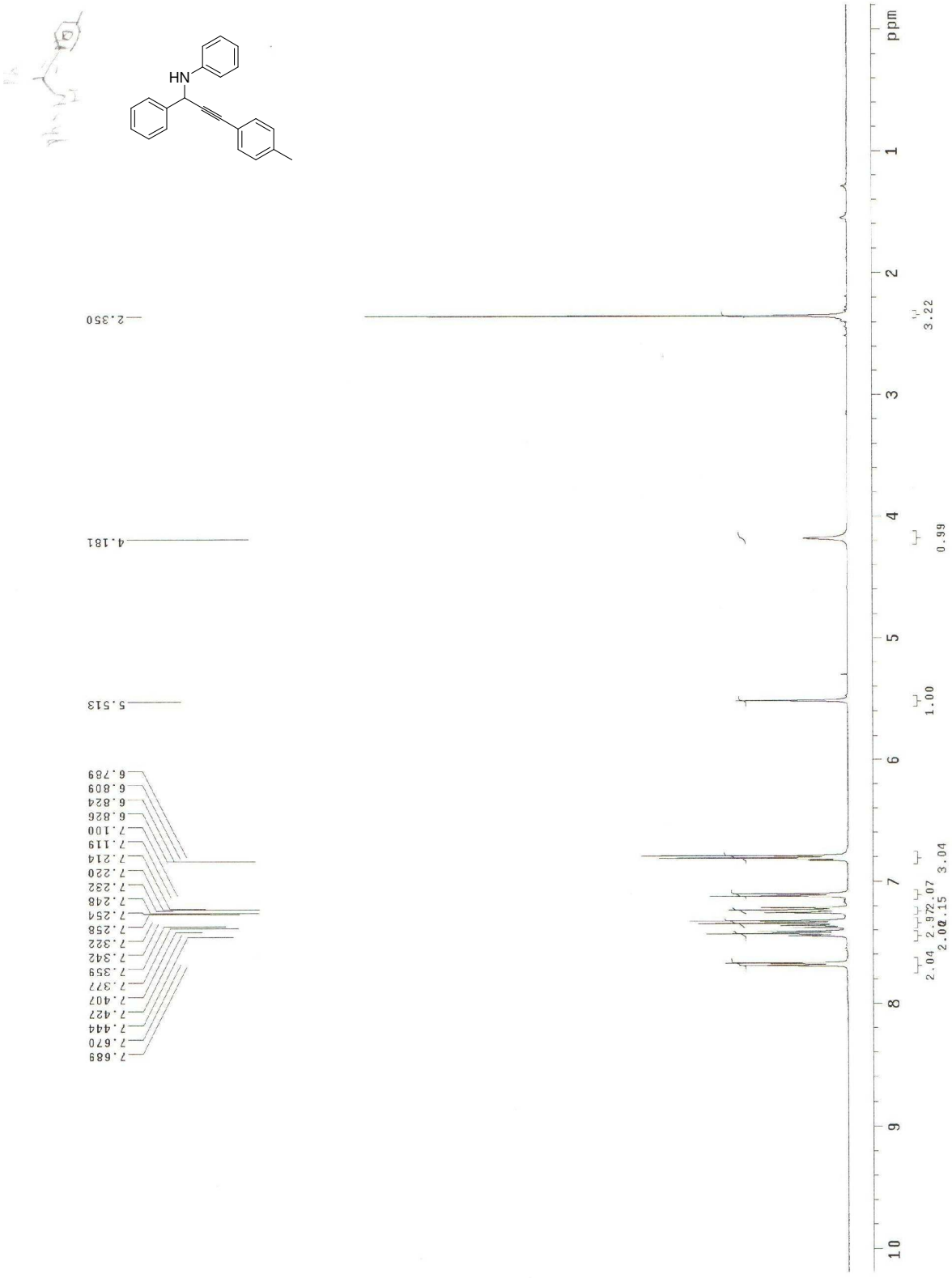
4-Bromopyridine-2,6-dicarboxylic acid bis[((*S*)-2-hydroxy-1-phenylethyl)amide] **(4)**



4-Bromo-2,6-bis[(*S*)-4-phenyloxazolin-2-yl]pyridine **(1)**



N-(1-Phenyl-3-p-tolyl-2-propynyl)-aniline (Table 1, entry 6)



N-(1-Phenyl-3-p-tolyl-2-propynyl)-aniline (Table 1, entry 6)