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New Synthetic Strategy toward Pyridine-Based Ligands for Supramolecular Chemistry Utilizing 2,6-Bis(trimethyltin)pyridine as the Central Building Block†

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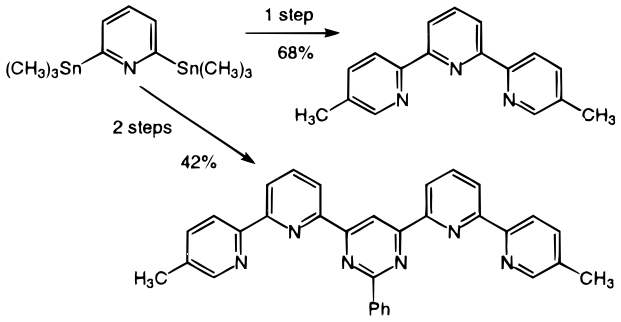
ABSTRACT



2,6-Bis(trimethyltin)pyridine was synthesized in high yields and multigram quantities and used for Stille-type coupling procedures to prepare 2,2′-bipyridines, 5,5″-dimethyl-2,2′:6′,2″-terpyridine, and 4,6-bis(5″-methyl-2″,2′-bipyrid-6′-yl)-2-phenylpyrimidine.

The preparation and application of organotin intermediates has become a very important aspect in organic heterocyclic chemistry and supramolecular science in the past two decades.[1] Many of the metallosupramolecular architectures used today are based on ligands which were synthesized utilizing Stille-type carbon−carbon bond-forming reactions and trialkyltin pyridine or bipyridine molecules.[2] However, the standard sequence for pyridines always requires the reaction of a bromopyridine with *n*-butyllithium at low temperatures followed by a reaction with trialkyltin chloride (see, e.g. Scheme 1; for methods using hexamethyldistannane, see, e.g. ref 3).

After a Stille-type cross-coupling utilizing palladium, the same sequence has to be repeated. Due to the butyllithium chemistry used, this multistep strategy is not applicable for many substituents or functional groups. However, application of bisorganotin-functionalized pyridine precursors opens a much more general synthetic pathway toward extended functional ligands. We describe here a new synthetic strategy developed during our research in the direction of extended

† This paper is dedicated to Professor F. Vögtle of the Universität Bonn on the occasion of his 60th birthday.

(1) Neumann, W. P. *The Organic Chemistry of Tin*, Wiley: New York, 1970. Stille, J. K. *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. Davies, A. G. *Organotin Chemistry*; Wiley-VCH: New York, 1997.

(2) See, e.g.: (a) Hanan, G. S.; Schubert, U. S.; Volkmer, D.; Riviere, E.; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. *Can. J. Chem.* **1997**, *75*, 169. (b) Schubert, U. S.; Weidl, C. H.; Lehn, J.-M. *Design. Monom. Polym.* **1999**, *2*, 1.

(3) Benaglia, M.; Toyota, S.; Woods, C. R.; Siegel, J. S. *Tetrahedron Lett.* **1997**, *38*, 4737.

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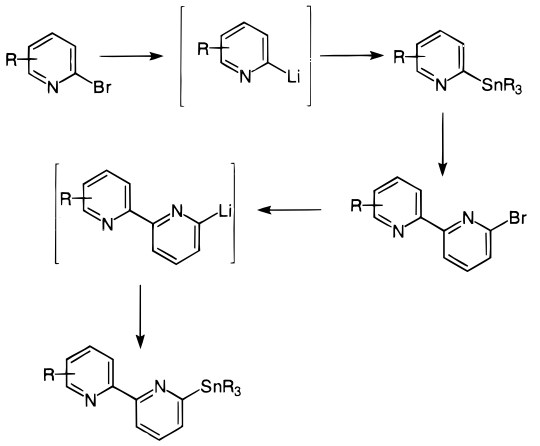
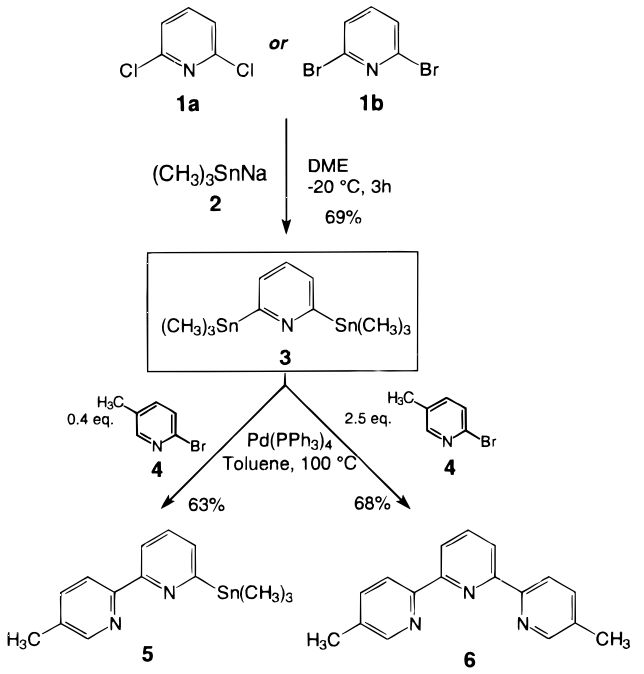
Scheme 1



Scheme 2



metallosupramolecular assemblies and polymers with grid-like architectures utilizing 2,6-bis(trimethyltin)pyridine as central building block.

The preparation of 2,6-bis(organotin)pyridine derivatives has always been a difficult and challenging problem using the reaction of the corresponding 2,6-dibromopyridine with *n*-butyllithium at low temperatures. The recently described interesting 2,6-bis(tributyltin)pyridine was obtained in only 17% yield after a very time-consuming purification procedure.[2a] This low yield is due to a very complex mixture of intermediates during the lithiation reaction[4] (the use of 2,6-diiodopyridine also did not improve the yields). However, a different approach utilized sodium or lithium stannane as an organotin source as frequently applied for other heterocycle units, e.g., pyrimidines.[5] In the case of pyridine, to the best of our knowledge this approach has only been described in one communication, which is not recognized by most researchers[6] (for very recent results see also ref 7): Yamamoto et al. showed nearly two decades ago that 2,6-bis(trimethyltin)pyridine could be synthesized by reacting sodium trimethylstannane (prepared in situ from trimethyltin chloride) with 2,6-dichloropyridine. After modification and optimization of the published procedure, we were able to synthesize 2,6-bis(trimethyltin)pyridine **3** on a 100 g scale in 69% yield starting from 2,6-dichloropyridine **1a** or 2,6-dibromopyridine **1b**[8] (Scheme 2). The product was easily isolated by extraction with diethyl ether and Kugelrohr distillation and stored at 0 °C for months. As a first application, we tried to use **3** in the preparation of the corresponding bipyridines and terpyridines. Reaction of **3** in a Stille-type coupling with 0.4 equiv of 2-bromo-5-methylpyridine **4** (synthesized from 2-amino-5-methylpyridine on a 100 g scale in 85% yield[9]) gave 6-trimethylstannyl-5′-methyl-2,2′-bipyridine **5** in 63% yield (Scheme 2).[10] This very important building block was again isolated by one extraction followed by a Kugelrohr distillation (the excess of **3** can be recycled). In contrast to the published three-step synthesis from **4** to the corresponding 6-tributylstannyl-2,2′-bipyridine using *n*-butyllithium, we were able to prepare the organotin-functionalized bipyridine in one step with significantly higher yields.[2a] Furthermore, **3** was reacted with a 2.5-fold excess of **4**, yielding 68% of the 5,5″-dimethyl-2,2′:6′,2″-terpyridine **6**[11] (see also ref 12 for a different synthetic approach).

Bipyridine **5** was then further coupled with 4,6-dichloro-2-phenylpyrimidine **7**[2a] to give 4,6-bis(5″-methyl-2″,2′-bipyrid-6′-yl)-2-phenylpyrimidine **8** in 66% yield (Scheme 3).[13]

(4) For investigations of the lithiation reaction, see, e.g.: Newkome, G. R.; Roper, J. M. *J. Organomet. Chem.* **1980**, *186*, 147. Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537.

(5) See, e.g.: Sandosham, J.; Undheim, K. *Tetrahedron* **1994**, *50*, 275.

(6) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 1731.

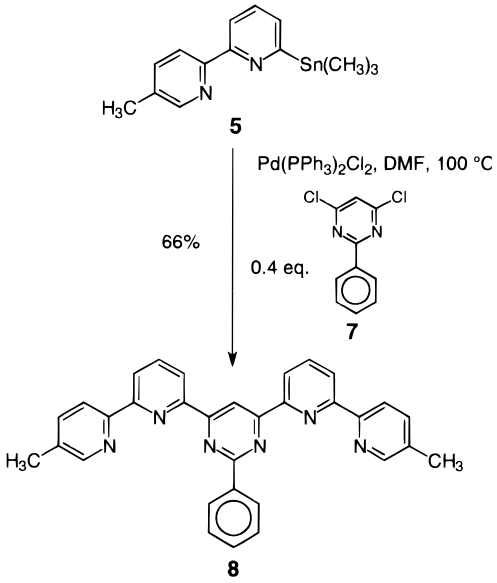
(7) Lehmann, U.; Henze, O.; Schlüter, A. D. *Chem. Eur. J.* **1999**, *5*, 854. Schubert, U. S.; Eschbaumer, C.; Weidl, C. H. *Synlett* **1999**, 342.

(8) To a suspension of freshly rasped sodium (50 g, 1.5 mol) in DME (500 mL) was added a solution of Me_3SnCl (100 g, 0.5 mol) in DME (175 mL) dropwise within 25 min while the temperature was kept below 0 °C. The temperature was lowered to −20 °C, and the mixture was stirred for 3 h. Excessive sodium was then removed by filtration, and a solution of **1a** (28.56 g, 0.193 mol) in DME (175 mL) was added. The reaction was stirred for 2 h and finally warmed to 25 °C. The solvent was removed in vacuo, and the residue was extracted with diethyl ether. After removal of the solvent, the crude product was purified by Kugelrohr distillation, yielding 53.9 g (69%) of **3**: colorless liquid, bp 100 °C (5×10^{-5} mbar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.21 (s, 18 H, H-7,7′), 7.15−7.20 (m, 3 H, H-3,4,5); MS (EI, 70 eV) *m*/*z* (%) = 390 (100) [$M^+ - CH_3$]. Anal. $C_{11}H_{21}NSn_2$ (404.38). Calcd: C, 32.64; H, 5.19; N, 3.46. Found: C, 32.77; H, 5.16; N, 3.51.

(9) Schubert, U. S.; Eschbaumer, C.; Hochwimmer, G. *Tetrahedron Lett.* **1998**, *39*, 8643. See also: Windscheif, P. M.; Vögtle, F. *Synthesis* **1994**, 87. Bolm, C.; Erhard, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.

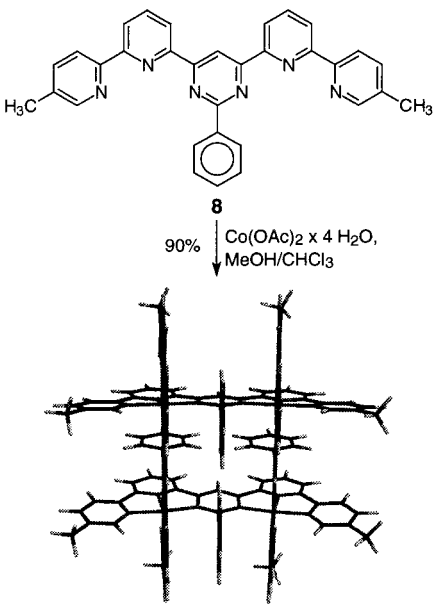
(10) Colorless liquid, bp 120 °C (5×10^{-5} mbar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.39 (s, 9 H, H-7), 2.37 (s, 3 H, H-7′), 7.42 (dd, 1 H, J = 7.26, 1.14 Hz, H-5), 7.59 (dd, 1 H, J = 8.01 Hz, 2.28, H-4′), 7.63 (t, 1 H, J = 7.23 Hz, H-4), 8.24 (dd, 1 H, J = 8.01 Hz, 1.14, H-3), 8.44 (d, 1 H, J = 8.37 Hz, H-3′), 8.48 (d, 1 H, J = 1.53 Hz, H-6′); MS (EI, 70 eV) *m*/*z* (%) = 319 (100) [$M^+ - CH_3$]. Anal. $C_{14}H_{18}N_2Sn$ (333.00). Calcd: C, 50.45; H, 5.41; N, 8.41. Found: C, 50.76; H, 5.28; N, 8.56.

Scheme 3



In contrast to published multistep procedures with rather low yields, we here describe a short multigram synthesis of this very interesting class of supramolecular ligands from commercially available starting materials in 30% overall yield. As the first application of this ligand, we synthesized the corresponding cobalt metal coordination array (Scheme 4, for general information see ref 14). Reaction with

Scheme 4



equimolar quantities of cobalt(II) acetate in methanol followed by an anion exchange gave the [2 × 2] cobalt(II) grid in 90% yield.[15] Investigations using MALDI-TOF mass spectrometry, UV/vis spectroscopy, and analytical ultracentrifugation revealed the successful formation of the metal coordination arrays and the exceptional stability of these new grids compared to those of the published systems.[16]

The described new synthetic strategy to extended pyridine-based supramolecular ligands opens new avenues for the use of such systems in supramolecular and polymer chemistry. 2,6-Bis(trimethyltin)pyridine was synthesized in high yields and multigram quantities as a new central building block. As first applications the 5-methyl-substituted bipyridines and terpyridines were synthesized as well as an extended metal coordination array-forming ligand. Further studies in this direction are currently in progress.

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(11) **3** (12.23 g, 30.2 mmol), **4** (13.00 g, 75.6 mmol), and [$Pd(PPh_3)_4$] (2.36 g, 2.03 mmol) were stirred in toluene at 110 °C for 96 h. The solvent was removed in vacuo and the residue treated with 6 M HCl (3 × 50 mL). The combined aqueous phases were washed with CH_2Cl_2 (3 × 30 mL), neutralized, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo, and the residue was recrystallized from ethyl acetate, yielding 5.44 g (68%) of **6**: white solid, mp 174−175 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.39 (s, 6 H, H-7,7″), 7.63 (dd, 2 H, 8.01 Hz, J = 2.28 Hz, H-4,4″), 7.91 (t, 1 H, J = 7.82 Hz, H-4′), 8.38 (d, 2 H, J = 7.62 Hz, H-3′,5′), 8.49 (d, 2 H, J = 8.40 Hz, H-3,3″), 8.50 (s, 2 H, H-6,6″); MS (EI, 70 eV) m/z (%) = 261 (100) [M^+]. Anal. $C_{17}H_{15}N_3$ (261.32). Calcd: C, 78.16; H, 5.75; N, 16.09. Found: C, 77.92; H, 5.73; N, 16.07.

(12) Schubert, U. S.; Eschbaumer, C.; Hochwimmer, G. *Synthesis* **1999**, 779.

(13) White solid, mp 259 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.37 (s, 6 H, H-7″), 7.57 (m, 3 H, H-m, p), 7.69 (dd, 2 H, J = 8.01, 2.28 Hz, H-4″), 8.04 (t, 2 H, J = 7.82 Hz, H-4′), 8.57 (m, 4 H, H-3″, 3′/5′), 8.69 (s, 2 H, H-6″), 8.72−8.79 (m, 4 H, H-o, 3′/5′), 9.64 (s, 1 H, H-5); MS (EI, 70 eV) m/z (%) = 492.1 (100) [M^+]; λ_{max} (CH_3CN)/nm (ϵ) 240 (46 200), 279 (35 800), 311 (15 800).

(14) Hanan, G. S.; Volkmer, D.; Schubert, U. S.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem.* **1997**, *109*, 1929; *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1842. Waldmann, O.; Hassmann, J.; Müller, P.; Hanan, G. S.; Volkmer, D.; Schubert, U. S.; Lehn, J.-M. *Phys. Rev. Lett.* **1997**, *78*, 3390. Waldmann, O.; Hassmann, J.; Koch, R.; Müller, P.; Hanan, G. S.; Volkmer, D.; Schubert, U. S.; Lehn, J.-M. *Mater. Res. Soc. Symp. Proc.* **1998**, *448*, 841. Waldmann, O.; Hassmann, J.; Müller, P.; Volkmer, D.; Schubert, U. S.; Lehn, J.-M. *Phys. Rev. B* **1998**, *58*, 3277. Schubert, U. S.; Lehn, J.-M.; Hassmann, J.; Hahn, C. Y.; Hallschmid, N.; Müller, P. In *Functional Polymers*; Patil, A. O., Schulz, D. N., Novak, B. M., Eds.; American Chemical Society: Washington, DC, 1998, ACS Symp. Ser. 704, p 248. Semenov, A.; Spatz, J. P.; Möller, M.; Lehn, J.-M.; Sell, B.; Schubert, D.; Weidl, C. H.; Schubert, U. S. *Angew. Chem.* **1999**, *111*, 2701; *Angew. Chem., Int. Ed.* **1999**, *38*, 2547.

(15) Prepared using $Co(OAc)_2 \cdot 4H_2O$ and a methanol/chloroform mixture as solvent followed by an anion exchange with NH_4PF_6 in 90% yield after recrystallization as brown crystals, mp > 300 °C: MALDI-TOF-MS 3075 [$M^+ - 2\ PF_6$], 2930 [$M^+ - 3\ PF_6$], 2785 [$M^+ - 4\ PF_6$], 2640 [$M^+ - 5\ PF_6$], 2495 [$M^+ - 6\ PF_6$], 2350 [$M^+ - 7\ PF_6$], 2205 [$M^+ - 8\ PF_6$]. Anal. $C_{128}H_{96}Co_4F_{48}N_3P_8$ (3365.77). Calcd ($\cdot 6H_2O$): C, 44.25; H, 3.05; N, 9.68. Found: C, 44.37; H, 3.15; N 9.67. λ_{max} (CH_3CN)/nm (ϵ): 239 (45 100), 279 (27 200), 360 (23 400).

(16) See, e.g.: Schubert, D.; Tziatzios, C.; Schuck, P.; Schubert, U. S. *Chem. Eur. J.* **1999**, *5*, 1377. Schubert, U. S.; Eschbaumer, C.; An, Q.; Salditt, T. *Polym. Prepr. (ACS)* **1999**, *40(1)*, 414.