High Yield Synthesis of 5,5'-Dimethyl-2,2'-bipyridine and 5,5''-Dimethyl-2,2':6',2''-terpyridine and Some Bisfunctionalization Reactions Using *N*-Bromosuccinimide

Ulrich S. Schubert,* Christian Eschbaumer, Georg Hochwimmer

Lehrstuhl für Makromolekulare Stoffe, Technische Universität München, Lichtenbergstr. 4, D-85747 Garching, Germany
Fax +49(89)28913562; E-Mail: schubert@makroserv.tech.chemie.tu-muenchen.de

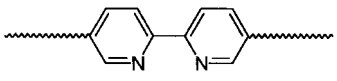
Received 12 October 1998

Dedicated to Professor Dr. Dieter Schubert on the occasion of his 60th birthday

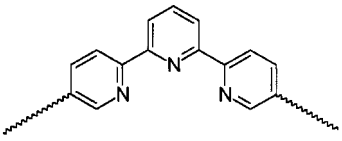
Abstract: 5,5'-Dimethyl-2,2'-bipyridine and 5,5''-dimethyl-2,2':6',2''-terpyridine were synthesized in multigram quantities in high yields utilizing organotin intermediates and Stille coupling procedures. The obtained ligands were dibrominated using *N*-bromosuccinimide.

Key words: 2,2'-bipyridines, 2,2':6',2''-terpyridines, Stille coupling, organotin intermediates, radical bromination

Since 1980, many highly ordered metallo-supramolecular architectures were obtained using the self-assembly of heterocyclic ligands with transition metal ions.[1] However, only a few heterocyclic systems fulfill the requirements for practical applications, such as formation of special architectures using recognition-directed self-assembly features, availability of the components in usable quantities, and possessing end groups which can be covalently incorporated into networks, assemblies or polymers. Some of the most prominent examples are the 5,5'-disubstituted oligo(2,2'-bipyridine) nickel(II) or iron(II) complexes with ethylene linkers between the bipyridine units[2,3] and the 5,5''-disubstituted-2,2':6',2''-terpyridine nickel(II) or iron(II) complexes with ethylene or methyleneoxymethylene linkers between the terpyidine units[4] due to their ability to spontaneously form well-defined double, triple or circular helical architectures (''helicates''). However, the multistep preparation of the basic unfunctionalized 5,5'-dimethyl-2,2'-bipyridine or 5,5''-dimethyl-2,2':6',2''-terpyridine ligands or its functionalized derivatives has always been the major drawback in the synthetic strategies towards these supramolecular building blocks.



5,5'-disubstituted 2,2'-bipyridine



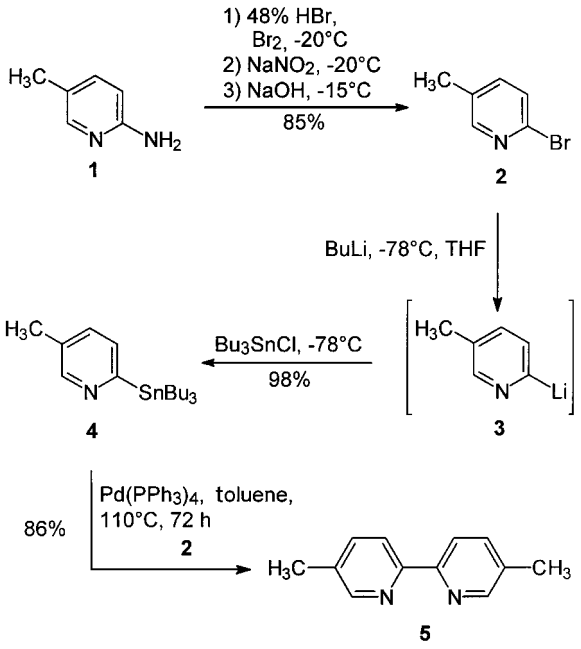
5,5''-disubstituted 2,2':6',2''-terpyridine

In contrast to the well established chemistry of the 6,6'-disubstituted bipyridines (synthesis of the 6,6'-dimethyl-2,2'-bipyridine on 100 g scale[5] and the functionalization via the *N*-oxide route and Boekelheide rearrangement[5a,6]) and the commercially available 4,4'-dimethyl-2,2'-bipyridine,[7] high yield synthetic routes towards the corresponding 5,5'-dimethyl compound are not described up to now. (However, a very elegant monofunctionalization was reported recently[8]). This is also the case for the corresponding 5,5'-dimethylterpyridine ligands. We describe here a new large scale approach towards 5,5'-disubstituted bipyridine and 5,5''-disubstituted terpyridine building blocks as well as the corresponding dibromination by radical bromination developed during our research in the direction of new metallo-supramolecular initiators for the living polymerization of oxazolines and related monomers.[9,10]

The synthesis of 5,5'-dimethyl-2,2'-bipyridine has been reported previously using classical coupling procedures starting from 3-picoline or 2-bromo-5-methylpyridine.[11] However, the yields obtained are rather low (0.5–36%) and the purification is sometimes very critical. We developed therefore a directed strategy using organotin intermediates and Stille coupling procedures.[12] Starting from the commercially available 2-amino-5-methylpyridine **(1)** the well-described 2-bromo-5-methylpyridine **(2)** could be synthesized in a 140 gram scale in 85% yield using a modified literature procedure[13] in a special 2 L glass reactor.

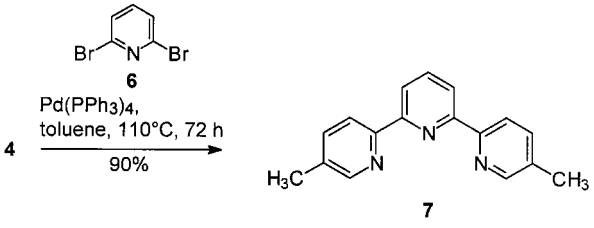
2-Bromo-5-methylpyridine **(2)** was then reacted with butyllithium at -78°C and the corresponding lithio compound **3** formed was directly treated with tributyltin chloride to yield 98% of 5-methyl-2-tributylstannyl pyridine **(4)**. The reaction was carried out in a 70 gram scale using Kugelrohr distillation for purification (for earlier preparations of **4** using the same strategy, see References 12,14). Stille-type coupling of **4** with 2-bromo-5-methylpyridine **(2)** yielded 86% of the 5,5'-dimethyl-2,2'-bipyridine **(5)** (72% overall yield starting from the commercially available **1**) (Scheme 1).

Using the same 5-methyl-2-tributylstannyl pyridine **(4)** the 5,5''-dimethyl-2,2':6',2''-terpyridine **(7)** can be obtained by cross-coupling with 2,6-dibromopyridine **(6)** (Scheme 2). A 2.5 times excess of **4** yielded 90% of the



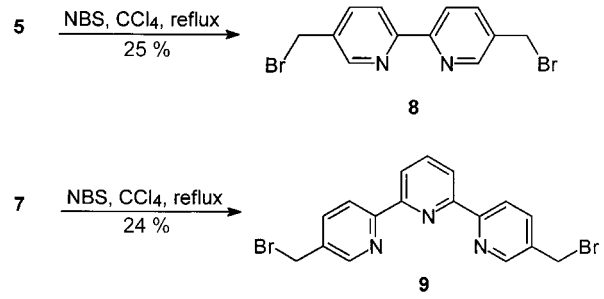
Scheme 1

corresponding terpyridine **7** (75% overall yield starting from the commercially available **1**). The isolation of **7** could be performed without column chromatography by separation of the starting materials and the organotin byproducts by acidification of the reaction mixture and subsequent extraction with organic solvents. Stannylpyridine **4**, 2,6-dibromopyridine **(6)**, and tributyltin bromide are extracted into the organic phase of a 6 M HCl/CH_2Cl_2 mixture, whereas the terpyridine **7** remains in the aqueous phase. After neutralization (pH 9) the crude terpyridine **7** was filtered off and recrystallized. This reaction sequence and the separation can also be performed in one step from **2**.



Scheme 2

The dimethyl-substituted ligands **5** and **7** can then be easily reacted with *N*-bromosuccinimide (NBS) to obtain the corresponding interesting building blocks 5,5'-bis(bromomethyl)-2,2'-bipyridine **(8)** and 5,5"-bis(bromomethyl)-2,2':6',2"-terpyridine **(9)** as shown in Scheme 3 (surprisingly we could not find full synthetic procedures, characterization data or information concerning the yields in the literature, even though the compounds have been used in several cases[15]). However, the yields are rather



low. Studies in this direction to develop new functionalization procedures are currently in progress (cf. References 9b, 9c).

Scheme 3

Reagents were obtained from commercial suppliers and used without further purification. THF was distilled under N_2 from potassium immediately prior to use in lithiation reactions. CH_2Cl_2 was dried over CaH_2. Organic extracts were dried over $MgSO_4$ or Na_2SO_4. Chromatography was carried out on Merck 60 silica gel (0.040–0.063 mm), Merck, activity II–III, alumina (0.063–0.200 mm). ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker AC 300 spectrometer in $CDCl_3$. The chemical shifts were calibrated to the residual solvent peak or TMS. Melting points were measured on a digital Mettler FP-5/FP-51 apparatus. Electronic absorption spectra were measured on a Varian Cary 3 spectrometer with λ in nm and ε ($\times 10^4$) in $M^{-1}cm^{-1}$.

2-Bromo-5-methylpyridine (2)

To a stirred aq HBr (48%, 500 mL) was added 2-amino-5-methylpyridine (**1**; 100 g, 0.926 mol) at 20–30°C. As soon as **1** had dissolved completely, the mixture was cooled to –20°C. The suspension was stirred and Br_2 cooled to -5°C (133 mL, 2.59 mol) was added dropwise. After stirring for 90 min at –20°C solution of $NaNO_2$ [170 g (2.46 mol) in H_2O (250 mL)] was added dropwise. The mixture was allowed to warm to r.t. and stirred for 1 h. The mixture was cooled to –20°C and NaOH [667 g (16.68 mol) in H_2O (1000 mL)] was added dropwise. The mixture was warmed to r.t. and extracted 6 times with Et_2O. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The solid was purified by sublimation resulting in 135 g (85%) of **2**; mp 39–40°C.

^1H NMR ($CDCl_3$): δ = 2.28 (3 H, s, H-7), 7.35 (2 H, m, H-3,4), 8.19 (1 H, s, H-6).

^{13}C NMR ($CDCl_3$): δ = 17.64 (C-7), 127.39 (C-3), 132.38 (C-5), 138.88 (C-2), 139.20 (C-4), 150.32 (C-6).

MS (EI, 70 eV): *m/z* (%) = 171 (44) [M^+], 92 (100) [M^+ – 79].

Anal. C_6H_6BrN (172.0): calcd C, 41.86; H, 3.49, Br, 46.45, N, 8.14; found: C, 41.76; H, 3.50; Br, 46.55; N, 8.19.

5-Methyl-2-tributylstannyl pyridine (4)

A solution of **2** (32.14 g, 0.187 mol) in THF (300 mL) was cooled to –78°C and BuLi (122 mL, 1.6 M in hexane, 0.195 mol) was added dropwise during 30 min. After stirring for further 90 min, Bu_3SnCl (60.5 mL, 0.224 mol) was added. The mixture was stirred for another 8 h at –78°C and was then allowed to warm to r.t. After adding H_2O (100 mL) the aqueous layer was extracted 4 times with Et_2O. The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The resulting liquid product was purified by Kugelrohr distillation to yield 70.59 g (98%) of **4**; bp 130°C/0.0038 Torr.

^{1}H NMR ($CDCl_3$): δ = 0.88 (9 H, t, *J* = 7.3 Hz, H-4'), 1.11 (6 H, t, *J* = 8.0 Hz, H-1'), 1.32 (6 H, tq, *J* = 7.25 Hz, H-3'), 1.56 (6 H, m, H-2'), 2.28 (3 H, s, H-7), 7.30 (2 H, m, H-3,4), 8.59 (1 H, s, H-6).

^{13}C NMR ($CDCl_3$): δ = 9.71 (C-1'), 13.63 (C-4'), 18.46 (C-7), 27.30 (C-3'), 29.06 (C-2'), 131.19 (C-5), 131.78 (C-3), 133.92 (C-4), 151.27 (C-6), 169.57 (C-2).

MS (EI, 70 eV): *m/z* (%) = 326 (50) [M^+ – 56], 268 (45) [M^+ – 114], 212 (100) [M^+ – 170].

Anal. $C_{18}H_{33}NSn$ (382.2): calcd C, 56.56; H, 8.64; N, 3.67; Sn, 31.08; found: C, 56.29; H, 8.84; N, 3.78; Sn, 31.09.

5,5'-Dimethyl-2,2'-bipyridine (5)

A mixture of 5-methyl-2-tributylstannyl pyridine (**4**; 12.13 g, 31.7 mmol), 2-bromo-5-methylpyridine **(2**; 4.64 g, 27.0 mmol) and $(Ph_3P)_4Pd$ (1.11 g, 0.96 mmol) in toluene was refluxed under N_2 for 3 d. The resulting brown mixture was evaporated in vacuo and the dark solid was dissolved in CH_2Cl_2. The organic phase was extracted 3 times with aq 6 M HCl. To recover the product from aq HCl, the combined aqueous layers were added dropwise to aq NH_3 (10%) under cooling. The solid formed was filtered, washed with aq NH_3, H_2O and purified by chromatography on silica gel with CH_2Cl_2 as eluent resulting in 4.27 g (86%) of a white solid; mp 114–115°C.

^{1}H NMR ($CDCl_3$): δ = 2.37 (6 H, s, H-7,7'), 7.60 (2 H, d, *J* = 8.2 Hz, H-4,4'), 8.24 (2 H, d, *J* = 8.0 Hz, H-3,3'), 8.48 (2 H, s, H-6,6').

^{13}C NMR ($CDCl_3$): δ = 18.29 (C-7,7'), 120.31 (C-3,3'), 133.01 (C-5,5'), 137.41 (C-4,4'), 149.48 (C-6,6'), 153.70 (C-2,2').

MS (EI, 70 eV): *m/z* (%): 184 (100) [M^+].

Anal. $C_{12}H_{12}N_2$ (184.1): calcd C, 78.23; H, 6.56; N, 15.20; found: C, 78.02; H, 6.54; N, 15.16.

5,5''-Dimethyl-2,2':6',2''-terpyridine (7)

A mixture of **4** (70.59 g, 0.185 mol), 2,6-dibromopyridine (**6**; 17.54 g, 0.074 mol) and $(Ph_3P)_4Pd$ (5.18 g, 4.48 mmol) in toluene (500 mL) were heated under reflux for 120 h. The solvent was removed in vacuo and the brown residue was treated with 6 M HCl (300 mL). The suspension was extraced with CH_2Cl_2 (1 × 500 mL, 4 × 200 mL) and the organic layers were washed with 6 M HCl (3 × 150 mL). The combined HCl solutions were treated with aq NH_3 (25%) and the pH adjusted to 9. The precipitate was separated, dissolved in CH_2Cl_2 and dried (Na_2SO_4). After removal of the solvent in vacuo the light yellow solid was recrystallized from EtOAc to afford **7** as a white solid; yield: 17.38 g (90%); mp 174–175°C.

IR (KBr): ν = 2916 w, 1591 w, 1557 s, 1484 m, 1443 m, 1375 w, 1257 w, 1132 m, 1024 m, 812 s, 754 m cm^{-1}.

UV/VIS (MeCN): λ_{max} (ε) = 245 (1.89), 286 (2.17).

^{1}H NMR ($CDCl_3$): δ = 2.39 (6 H, s, H-7,7",), 7.63 (2 H, d, *J* = 8.01 Hz, H-4,4"), 7.91 (1 H, t, *J* = 7.82 Hz, H-4'), 8.38 (2 H, d, *J* = 7.62 Hz, H-3',5'), 8.49 (2 H, d, *J* = 8.40 Hz, H-3,3"), 8.50 (2 H, s, H-6,6").

^{13}C NMR ($CDCl_3$): δ = 18.34 (C-7,7"), 120.32 (C-3,3"), 120.64 (C-3',5'), 133.32 (C-5,5"), 137.32 (C-4,4"), 137.70 (C-4'), 149.46 (C-6,6"), 153.75 (C-2,2"), 155.33 (C-2',6').

MS (EI, 70 eV): *m/z* (%) = 261 (100) [M^+], 233 (12) [M^+ – CHN], 219 (16) [M^+ – C_3H_6], 169 (14) [M^+ – C_6H_6N], 130 (10) [M^+ – 131].

Anal. $C_{17}H_{15}N_3$ (261.3): calcd C, 78.16; H, 5.75; N, 16.09; found C, 77.92; H, 5.73; N 16.07.

5,5'- Bis(bromomethyl)-2,2'-bipyridine (8)

A solution of **5** (0.57 g, 3.09 mmol), NBS (2.90 g, 16.3 mmol), and AIBN (78 mg, 0.48 mmol) in CCl_4 (50 mL) was refluxed under N_2 for 22 min and the precipitated succinimide was removed immediately from the hot mixture by filtration. The precipitate was washed with CCl_4 and the combined CCl_4 phases were evaporated. The remaining solid was dissolved in CH_2Cl_2 (100 mL) and extracted with 0.5 M $Na_2S_2O_3$ solution (2 ×150 mL). The combined $Na_2S_2O_3$ fractions were extracted with CH_2Cl_2 (50 × mL)and the combined CH_2Cl_2 layers were dried (Na_2SO_4). The crude product was recrystallized from CH_2Cl_2 yielding 0.293 g (28%) of a white powder. Further purification using column chromatography (silica gel, EtOAc/hexane, 1:4) yielded 0.26 g (25%) of very pure **8**; mp 193–194°C.

^{1}H NMR ($CDCl_3$): δ = 4.56 (4 H, s, H-7,7'), 7.96 (2 H, dd, 8.20 Hz, *J* = 2.29 Hz, H-4,4'), 8.55 (2 H, d, *J* = 8.39 Hz, H-3,3'), 8.74 (2 H, s, H-6,6').

^{13}C NMR ($CDCl_3$): δ = 29.46 (C-7,7'), 121.24 (C-3,3'), 133.97 (C-5,5'), 137.71 (C-4,4'), 149.27 (C-6,6'), 155.21 (C-2,2').

MS (EI, 70 eV), *m/z* (%) = 341 (24) [M^+].

Anal. $C_{12}H_{10}Br_2N_2$ (342.0): Calc. C, 42.14; H, 2.95; N, 8.19; found: C, 42.39; H, 3.14; N, 8.07.

5,5''-Bis(bromomethyl)-2,2':6',2''-terpyridine (9)

A mixture of **7** (2.27 g, 8.69 mmol), NBS (7.75 g, 43.5 mmol) and AIBN (221 mg, 1.35 mmol) in CCl_4 (120 mL) was refluxed under N_2 for 32 min and the precipitated succinimide was removed immediately from the hot mixture by filtration. The precipitate was washed with CCl_4, the combined CCl_4 phases were reduced to 50 mL in vacuo and the precipitate was removed by filtration. The solid was dissolved in CH_2Cl_2 (100 mL) and extracted with 0.5 M $Na_2S_2O_3$ solution (2 × 150 mL). The combined $Na_2S_2O_3$ fractions were extracted with CH_2Cl_2 (50 mL) and the combined CH_2Cl_2 layers were dried (Na_2SO_4) yielding 870 mg (24%) of **9** after recrystallization from $CHCl_3$; mp 195–196°C.

^{1}H NMR ($CDCl_3$): δ = 4.56 (4 H, s, H-7,7"), 7.92 (2 H, dd, *J* = 8.39, 2.29 Hz, H-4,4"), 7.97 (1 H, t, *J* = 8.01 Hz, H-4'), 8.47 (2 H, d, *J* = 8.02 Hz, H-3',5'), 8.61 (2 H, d, *J* = 8.01 Hz, H-3,3"), 8.72 (2 H, d, *J* = 2.29 Hz, H-6,6").

^{13}C NMR ($CDCl_3$): δ = 29.54 (C-7,7"), 121.24 (C-3,3"), 121.55 (C-3',5'), 133.87 (C-5,5"), 137.79 (C-4,4"), 138.08 (C-4'), 149.06 (C-6,6"), 154.61 (C-2,2"), 155.78 (C-2',6').

MS (EI, 70 eV), *m/z* (%) = 419 (20) [M^+].

Anal. $C_{17}H_{13}Br_2N_3$ (419.1): calcd C, 48.72; H, 3.13; N, 10.03; found: C, 48.63; H, 2.68; N, 10.05.

Acknowledgement

This study was supported by the Bayerisches Staatsministerium für Unterricht, Kultus, Wissenschaft und Kunst, the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie. We thank Reilly Tar & Chem. Corp. for contributing **1** and Prof. Dr.-Ing. Oskar Nuyken for his support.

References

(1) (a) Lehn, J.-M. *Supramolecular Chemistry - Concepts and Perspectives*, VCH: Weinheim, Germany, 1995.
(b) Whitesides, G.M.; Mathias, J.P.; Seto, C.T. *Science* **1991**, *254*, 1312.
(c) Lawrence, D.S.; Jiang, T.; Levett, M. *Chem. Rev*. **1995**, *95*, 2229.
(d) Newkome, G.R.; Cardullo, F.; Constable, E.C.; Moorefield, C.N.; Cargill Thompson, A.M.W. *J. Chem. Soc., Chem. Commun.* **1993**, 925.

(2) Krämer, R.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Angew. Chem.* **1993**, *105*, 764; *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 703.

Krämer, R.; Lehn, J.-M.; Marquis-Rigault, A. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5394.
(3) Hasenknopf, B.; Lehn, J.-M.; Kneisel, B.O.; Baum, G.; Fenske, D. *Angew. Chem.* **1996**, *108*, 1987; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1838.
(4) (a) Constable, E.C. Prog. *Inorg. Chem.* **1994**, *42*, 67.
(b) Piguet, C.; Hopfgarten, G.; Bocquet, B.; Schaad, O.; Williams, A.F. *J. Am. Chem. Soc.* **1994**, *116*, 9092.
(c) Potts, K.T.; Keshavarz-K, M.; Tham, F.S.; Abruña, H.D., Arana, C.R. *Inorg. Chem.* **1993**, *32*, 4436.
(d) Crane, J.D.; Sauvage, J.P. *New J. Chem.* **1992**, *16*, 649.
(5) (a) Newkome, G.R.; Puckett, W.E.; Kiefer, G.E.; Gupta, V.K.; Xia, Y.-J.; Coreil, M.; Hackney, M.A. *J. Org. Chem.* **1982**, *47*, 4116.
(b) Newkome, G.R.; Gupta, V.K.; Fronczek, F.R. *Inorg. Chem.* **1983**, *22*, 171.
(c) Rodriguez-Ubis, J.-C.; Alpha, B.; Plancherel, D.; Lehn, J.-M. *Helv. Chim. Acta* **1984**, *67*, 2264.
(d) Rode T.; Breitmaier, E. *Synthesis* **1987**, 574.
(e) Harding, M.M.; Koert, U.; Lehn, J.-M.; Marquis-Rigault, A.; Piquet, C.; Siegel, J. *Helv. Chim. Acta* **1991**, *74*, 594.
(f) Eisenbach, C.D.; Göldel, A.; Terskan-Reinold, M.; Schubert, U.S. In *Polymeric Materials Encyclopedia*, Salamone, J.C., Ed.; CRC Press: Boca Raton, 1996, pp 8162-8172.
(6) (a) Eisenbach C.D.; Schubert, U.S. *Macromolecules* **1993**, *26*, 7372.
(b) Eisenbach, C.D.; Göldel, A.; Terskan-Reinold, M.; Schubert, U.S. *Macromol. Chem. Phys*. **1995**, *196*, 1077.
(c) Eisenbach, C.D.; Schubert, U.S.; Baker, G.R.; Newkome, G.R. *J. Chem. Soc., Chem. Commun.* **1995**, 69.
(7) e.g., from Aldrich or Reilly Tar & Chem. Corp.
(8) Newkome, G.R.; Groß, J.; Patri, A.K. *J. Org. Chem.* **1997**, *62*, 3013.
(9) (a) Hochwimmer, G.; Nuyken, O.; Schubert, U.S. *Macromol. Rapid Commun.* **1998**, *19*, 309.
(b) Schubert, U.S.; Nuyken, O.; Hochwimmer, G. *Division of Polymeric Materials: Science and Engineering (ACS)* **1998**, 79, 11.
(c) Schubert, U.S.; Eschbaumer, C.; Hochwimmer, G. *Tetrahedron Lett*., **1998**, *39*, 8643.
(10) See also: Lamba, J.J.S.; Fraser, C.L. *J. Am. Chem. Soc.* **1997**, *119*, 1801.
(11) (a) Sasse, W.H.F. *Org. Synth.* **1966**, *46*, 5.
(b) Sasse, W.H.F.; Whittle, C.P. *J. Chem. Soc*. **1961**, 1347.
(c) Polin, J.; Schmohel, E.; Balzani, V. *Synthesis* **1998**, 321.
(12) For a recent example, see: Hanan, G.S.; Schubert, U.S.; Volkmer, D.; Riviere, E.; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. *Can. J. Chem.* **1997**, *75*, 169.
(13) Windscheif, P.M.; Vögtle, F. *Synthesis* **1994**, 87.
(14) Bolm, C.; Erhard, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.
(15) (a) Ebmayer, F.; Vögtle, F. *Chem. Ber*. **1989**, *122*, 1725.
(b) Hamilton, A.D.; Rubin, H.-D.; Bocarsly, A. *J. Am. Chem. Soc.* **1984**, *106*, 7255.
(c) Hasenknopf, B.; Lehn, J.-M.; Baum, G.; Fenske, D. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 1397.

Article Identifier:
1437-210X,E;1999,0,05,0779,0782,ftx,en;H09798SS.pdf