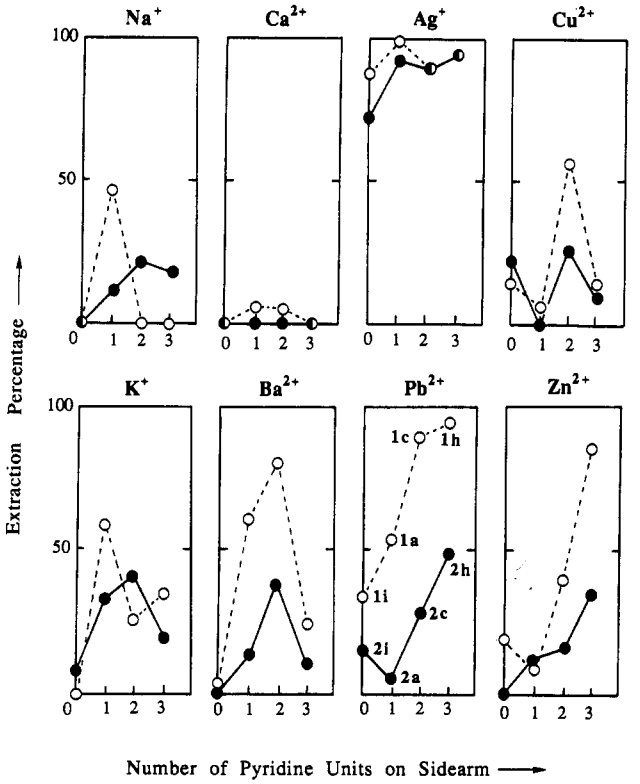


Figure 1. Side arm effect on cation extraction abilities of double-armed crown ethers (–O–) and lariat ethers (–●–). Number of pyridine units: 0 (**1i**, **2i**); 1 (**1a**, **2a**); 2 (**1c**, **2c**); 3 (**1h**, **2h**). See graph for Pb^{2+} case.

cations in the aqueous phase which were spectroscopically determined.

Figure 1 compares side arm effects on the cation-extraction abilities of double-armed crown ethers with those of lariat ethers, in which extraction percentages of several metal cations are plotted with the number of pyridine units on the side arms of diaza-crown ethers (**1a**, **1c**, **1h**, and **1i**) and aza-crown ethers (**2a**, **2c**, **2h**, and **2i**). Cation-extraction abilities of these crown ethers were apparently dependent on the number of pyridine units on the single arm, and arm functionalization generally enhanced the extraction abilities of parent diaza-18-crown-6 and aza-18-crown-6. When Ca^{2+}, Ba^{2+}, Ag^{+}, Pb^{2+}, Cu^{2+}, and Zn^{2+} cations were chosen as guest cations, double-armed crown ethers exhibited curved plots similar to those observed with lariat ethers. Typically, bipyridine-armed crown ethers **1c** and **2c** exhibited higher extraction activities for Ba^{2+} and Cu^{2+} cations than monopyridine- and terpyridine-armed crown ethers **1a**, **1h**, **2a**, and **2h**. As schematically shown in Figure 2, double-armed crown ethers have various kinds of cation-binding modes: only one side arm interacts with guest metal cation (type A); two side arms provide coordination from the same or opposite sides (type B or C); and others. The present observations support the possibility of type A for these metal cations, which may exhibit similar binding profiles to the lariat ether complexation (type D). Since double-armed crown ethers showed higher extractabilities than lariat ethers, two functionalized side arms of the double-armed crown ethers may offer a statistical advantage for cooperative binding of these metal cations. For Na^{+} and K^{+} cations, double-armed crown ethers provided different side arm effects from those with lariat ethers. This probably suggests that the double-armed crown ethers

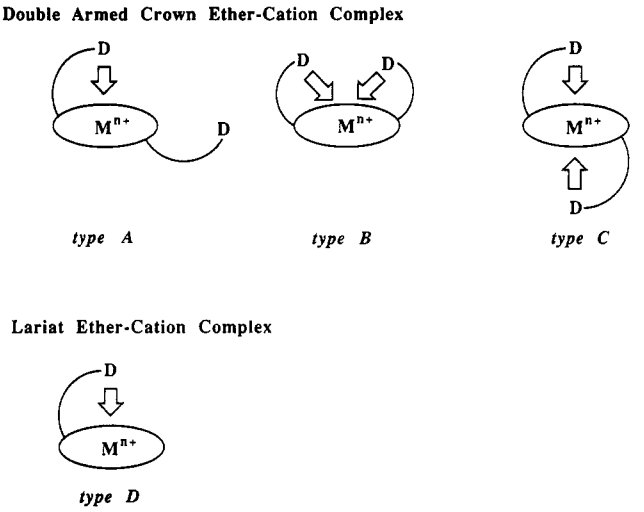


Figure 2. Cation binding modes of double-armed crown ether and lariat ether.

would form the complexes of type B or C. It is noted that when the total number of donor atoms available was 8, both series displayed peak extractability. A similar peak binding property has been reported in the polyether-functionalized lariat ethers by Gokel et al.[9] Aza- and diaza-crown rings are directed by the guest cation to envelop and solvate in the geometry most appropriate for the cation.

Table I summarizes cation extraction properties of the armed crown ethers employed. This indicates that the oligopyridine-functionalized side arms are useful as secondary binding sites for various metal cations. Indeed, double-armed crown ethers having bipyridine-functionalized side arms **1c–g** exhibited higher extraction abilities than simple diaza-crown ethers **1i** and **1j**. Their extraction profiles were interestingly dependent on the structures of the bipyridine units introduced, though they were substantially controlled by the ring sizes of the parent diaza-18-crown-6.[10] Double-armed crown ethers **1c** and **1d** extracted Ba^{2+} cation efficiently, while crown ethers **1f** and **1g** favored Cu^{2+} and Zn^{2+} ions. Bipyridine-armed diaza-crown ether **1e**, which has structural elements the same as but ligand geometry different from **1c**, was examined for comparison. This rarely extracted the alkali and alkaline earth metal cations. Since dipyridylmethyl derivative **4** showed greatly different guest selectivity from those of pyridine- and bipyridine-armed crown ethers **1a** and **1c**, geometrical arrangement of pyridine units on the side arm should be seriously considered in the design of an effective cation binder of this type. Terpyridine-armed diaza-crown ether **1h** exhibited lower extraction abilities for Na^{+}, K^{+}, Ca^{2+}, and Ba^{2+} cations than did double-armed crown ether **1a** and for Ba^{2+} and Cu^{2+} cations than did crown ether **1c**. The terpyridine has more pyridine–nitrogen donor atoms, but they are probably placed at less favorable positions to provide effective coordination of these metal cations trapped in the diaza-18-crown-6 ring. The bulky and rigid side arm is sometimes more of a hindrance than an asset. Coordination character and steric effects of the oligopyridine group clearly influenced cooperative binding modes and determined metal selectivity.

(9) Schultz, R. A.; White, B. D.; Dishong, D. M.; Arnold, K. A.; Gokel, G. W. *J. Org. Chem.* **1985**, *107*, 6659.
(10) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1991**, *91*, 1721.

Table I. Cation Extraction Properties of Armed Aza-Crown Ethers[a]

	extraction percentage (%)									
crown	Li^+	Na^+	K^+	Ag^+	Mg^{2+}	Ca^{2+}	Ba^{2+}	Pb^{2+}	Cu^{2+}	Zn^{2+}
1a	*	47	59	99	*	6	61	54	6	9
1b	4	10	60	99	*	*	35	(80)	44	(11)
1c	4	*	25	90	*	6	80	90	57	(39)
1d	*	*	46	89	*	*	(76)	(83)	20	9
1e	(*)	(*)	(*)	93	*	(*)	(*)	(63)	47	(51)
1f	*	*	25	98	*	*	13	76	(73)	41
1g	*	*	23	93	*	*	10	(80)	62	35
1h	*	*	35	95	*	*	24	(95)	14	86
1i	*	*	*	89	*	*	4	34	14	19
1j	*	*	3	96	*	*	20	41	13	20
2a	13	12	33	92	*	*	13	5	*	12
2c	*	21	41	90	*	*	38	29	26	16
2h	*	19	20	95	*	*	11	49	10	35
2i	*	*	*	73	*	(*)	*	15	(22)	*
3c	*	*	*	(100)	*	*	*	(92)	(65)	9
3h	*	*	*	(100)	*	*	*	(99)	(100)	48
4	*	24	54	100	*	81	83	84	99	68

[a] Parentheses indicate that a considerable amount of precipitate was observed. An * indicates a percentage ≤3%.

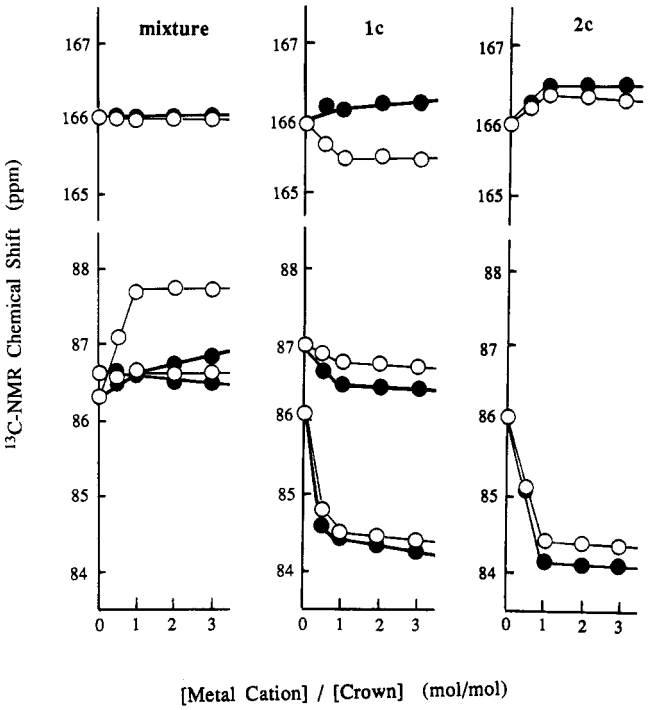


Figure 3. K^+- and Ba^{2+}-induced changes in ^{13}C NMR chemical shifts of a mixture (diaza-18-crown-6:bipyridine = 1:2) and crown ethers **1c** and **2c**: –○–, Ba^{2+} ion; –●–, K^+ ion. Chemical shift indicated was determined by using the peak of the DMF carbonyl carbon (δ_C 180.00 ppm) as reference.

Thia-analogs **3c** and **3h** were characterized by soft donor atoms both on the side arm and parent thia-crown ring.[11] Although these efficiently extracted soft Ag^+, Pb^{2+}, and Cu^{2+} cations, they rarely bound hard alkali and alkaline earth metal cations. A combination of parent crown structure and cation-ligating side arm should be adjusted to a target metal cation.

^{13}C-NMR Binding Studies. Further information on cation-binding behavior of the armed crown ether was obtained via ^{13}C-NMR spectroscopy in DMF/D_2O (4/1) solution. Figure 3 illustrates the K^+- and Ba^{2+}-induced changes in the ^{13}C-NMR chemical shifts of selected carbon signals of double-armed crown ether **1c** and lariat ether **2c**, comparing them with those of a mixture of unsubstituted diaza-18-crown-6 and bipyridine (1/2 = mol/mol).

Bipyridine-armed diaza-18-crown-6 **1c** was confirmed to wrap Ba^{2+} cation very nicely in a three-dimensional fashion. Actually, the addition of $Ba(ClO_4)_2$ salt to the crown ether **1c** solution offered significant changes upon 1:1 complexation. Several signals for the carbons on the bipyridine-ring and parent crown-ring shifted greatly, indicating that cooperative action of these two binding sites was involved in encapsulation of the guest Ba^{2+} cation. Since some carbon signals broadened at stoichiometries below 1:1 (metal/crown), the guest Ba^{2+} cation was thought to be rigidly complexed and to be slowly exchanged. In contrast, the addition of $KClO_4$ salt modestly influenced bipyridine-ring signals of the crown **1c**, though continuous and large shifts were observed for signals of crown ring carbons. This may indicate that bipyridine-functionalized side arms loosely interact with K^+ cation giving a different type of coordination from that observed with the Ba^{2+} ion. Ba^{2+} and K^+ cations have similar ion sizes, but their charge numbers greatly influenced complex structures and binding kinetics. In other words, bipyridine-armed diaza-crown ether **1c** distinguished Ba^{2+} cation from K^+ cation.

Figure 3 also indicates that bipyridine-armed lariat ether **2c** forms 1:1 complexes with K^+ and Ba^{2+} cations and that its binding modes are similar. Since aza-18-crown-6 ring is more flexible than diaza-18-crown-6 ring, the lariat ether **2c** can adjust its conformation to the effective cooperative binding of the bipyridine unit and aza-crown ring. The ^{13}C-NMR spectrum of a mixture of unsubstituted diaza-18-crown-6 and bipyridine changed in the presence of K^+ and Ba^{2+} cations, but only slight changes were observed for bipyridine-ring carbon signals in the presence of both metal cations (see Figure 3). Thus, free bipyridine unit was confirmed to rarely coordinate the metal cation trapped in the diaza-crown ring.

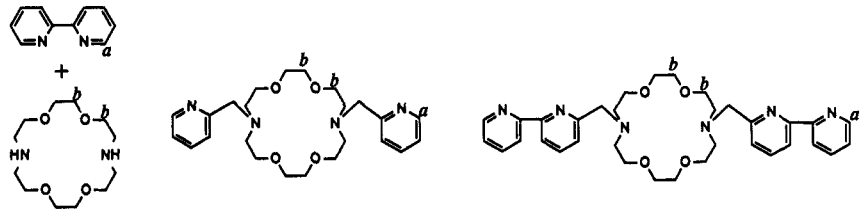
Table II summarizes the results of ^{13}C-NMR binding studies for double-armed diaza-crown ethers **1a** and **1c**, lariat ethers **2a** and **2c**, and a mixture of diaza-18-crown-6 and bipyridine (1/2 = mol/mol). Bipyridine-armed diaza-crown ether **1c** effectively formed three-dimensional complexes with Ag^+, Ba^{2+}, Pb^{2+}, and Zn^{2+} cations, while pyridine-armed crown ether **1a** encapsulated Na^+ and K^+ cations as well as Ag^+, Ba^{2+}, and Zn^{2+} cations. The metal cations, which were accommodated nicely in a three-dimensional fashion, were confirmed to be effectively

(11) Buschmann, H. J. In *Stereochemical and Stereophysical Behavior of Macrocycles*; Elsevier: New York, 1987; p 103.

Table II. Guest-Induced Changes in ^{13}C-NMR Chemical Shifts of Double-Armed Crown Ethers[a]

		induced chemical shift (ppm)							
crown	carbon[b]	Li^+	Na^+	K^+	Ag^+	Ca^{2+}	Ba^{2+}	Pb^{2+}	Zn^{2+}
mixture	a	−0.1	*	*	*	*	*	*	−0.9
	b[c]	−0.2	*	*	−0.8	−0.6	0.7	−0.1	1.0
1a	a	*	1.2	0.9	2.6	0.2	0.9	0.1	−0.9
	b[c]	−0.1	−1.9	−1.0	−1.6	−1.2	−0.9	−1.2	−1.7
1c	a	*	0.2	0.2	0.8	0.2	−0.5	0.5	*d*
	b[c]	*	−0.8	−1.1	−1.2	−1.1	−0.9	−3.0	*d*
2a	a	0.1	1.5	1.1	2.1	0.9	0.6	−0.3	−0.7
	b	−0.5	−2.5	−1.6	−2.8	−2.1	−1.1	−1.2	−3.9
2c	a	*	0.3	0.5	1.9	0.7	0.4	0.7	−2.6
	b	−0.1	−1.6	−1.9	−1.4	−1.4	−1.6	−1.5	−3.5

[a] Conditions: crown, 0.025 mmol: guest perchlorate, 0.025 mmol in DMF-D_2O (4:1) 0.5 mL. Positive is downfield shift. An * indicates a shift $<\pm 0.1$ ppm. [b] See structural formulas as described below. [c] Averaged values of two carbon signals. [d] They were broadening and disappeared.



mixture 1a 1c

2a 2c

extracted (see Table I). Similar phenomena were observed in the lariat ethers **2a** and **2c** systems.

The spectral changes at the stoichiometries below 1:1 (metal/crown) provide kinetic information (on the NMR time scale) of cation-exchange process: (i) slow exchange (rigid complexation); some ^{13}C-NMR signals broaden, split, or disappear in the presence of excess crown; (ii) fast exchange (flexible complexation); averaged signals are recorded over a wide range of metal/crown ratio. We found that double-armed crown ethers **1a** and **1c** formed kinetically slow complexes with Ag^+, Ba^{2+}, Pb^{2+}, and Zn^{2+} cations, while lariat ethers **2a** and **2c** offered rigid complexation with Ba^{2+}, Pb^{2+}, and Zn^{2+} cations. Cooperative binding of the functionalized side arm and the parent crown ring tends to form kinetically slow (rigid) complexes with divalent metal cations.[12] Since such slow kinetics were rarely observed in the mixture of unsubstituted diaza-crown and bipyridine, side arm participation had great influence on cation-binding kinetics as well as on cation-binding strength.

Cation Transport across a Liquid Membrane. Using new armed crown ethers as synthetic carriers, transport experiments were carried out in a CH_2Cl_2 liquid membrane system. Table III summarizes the transport properties of double-armed diaza-crown ethers and lariat ethers, together with those of reference crown ethers.

Oligopyridine-functionalized double-armed crown ethers **1a–d** and **1f–h** and lariat ethers **2a–h** generally exhibited higher transport abilities than simple crown ethers **1i**, **1j**, and **2i**. Interestingly, the guest selectivity of the transport process was somewhat different from that of the extraction process. Enhanced transport was observed especially for alkali and alkaline earth metal cations, though the nature of the oligopyridine substituent greatly influenced details of the transport profiles. All the crown ethers employed quantitatively extracted Ag^+ and Pb^{2+} cations (see Table I), but were unable to act as effective carriers of these heavy metal cations. For example, bipyridine-armed diaza-crown ether **1c** exhibited large transport rates for Na^+ and K^+ cations, while it extracted Ag^+, Ba^{2+}, and Pb^{2+} cations more effectively. Terpyridine-armed diaza-crown ether **1h** efficiently carried Ba^{2+} cation which was modestly extracted. As frequently reported in the carrier-mediated transport systems,[13] a guest cation which was complexed moderately/loosely with a carrier was smoothly transported. Thus, complete encapsulation of heavy and transition metal cations by the armed crown ether is appropriate for effective extraction but not for fast transport. Oligopyridines were well recognized as powerful chelating functions for soft metal cations, but combination of oligopyridine-functionalized side arm and aza-crown ether offered higher carrier activities for hard metal cations than for soft metal cations.

Summary. We have developed a new series of double-armed crown ethers and lariat ethers having oligopyridine-functionalized side arms. Although several crown ethers incorporating bipyridine functions have been well characterized as potential ligands of heavy, transition, and

(12) In each spectrum, a broadened or split signal was not observed at 1:1 stoichiometry except for the crown **1c**–Zn^{2+} system, indicating that interconversions between complexes of types **A**, **B**, and **C** as illustrated in Figure 2 would be rapid if they occurred.

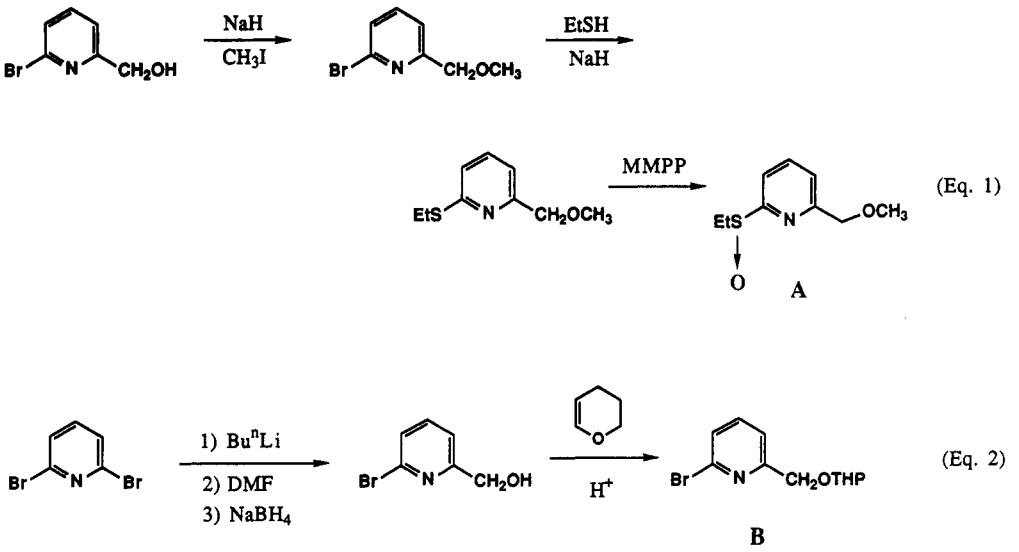
(13) (a) Lamb, J. D.; Christensen, J. J.; Oscarson, J. L.; Nielson, B. L.; Asay, B. W.; Izatt, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 6820. (b) Behr, J. P.; Kirch, M.; Lehn, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 241. (c) Yoshida, S.; Hayano, S. *J. Am. Chem. Soc.* **1986**, *108*, 3903. (d) Tsukube, H.; Adachi, H.; Morosawa, S. *J. Org. Chem.* **1991**, *56*, 7102.

Table III. Cation-Transport Properties of Armed Aza-Crown Ethers[a]

	transport rate ×10⁶ (mol/h)												
crown	Li^+	Na^+	K^+	Cs^+	Ag^+	Mg^{2+}	Ca^{2+}	Ba^{2+}	Pb^{2+}	Cu^{2+}	Ni^{2+}	Co^{2+}	Zn^{2+}
1a	5.0	10.5	7.9	7.3	*	*	11.5	3.4	1.6	2.2	*	0.8	4.1
1b	2.3	12.1	2.3	(4.4)	0.7	*	0.7	5.4	1.5	3.6	*	*	*
1c	6.0	10.3	10.9	3.9	0.8	*	3.4	1.6	*	(1.1)	*	(*)	*
1d	1.7	4.1	5.4	1.8	(2.8)	*	*	(2.9)	(*)	(*)	*	*	*
1e	*	0.5	3.4	*	(*)	*	*	0.4	*	*	(*)	*	*
1f	0.7	1.2	3.7	2.7	(*)	*	*	3.5	*	*	*	*	*
1g	0.8	3.5	10.9	2.5	0.8	*	*	5.0	(3.7)	(*)	(*)	*	(*)
1h	0.6	3.9	7.2	4.0	0.5	*	0.7	10.5	0.5	(*)	*	*	*
1i	*	2.4	6.8	1.2	*	*	*	2.4	2.9	(*)	*	*	(*)
1j	*	2.0	6.7	0.4	*	*	*	2.7	2.7	*	*	*	*
2a	1.7	8.3	8.9	6.5	*	*	0.6	3.1	2.3	1.8	1.0	0.6	0.4
2c	3.7	6.7	6.5	2.1	0.6	*	2.0	2.3	1.2	2.0	*	0.4	0.4
2h	(*)	4.5	7.0	1.6	0.9	*	0.4	5.2	0.8	1.6	*	*	*
2i	*	1.8	9.4	2.4	2.2	*	*	5.5	2.5	*	*	*	*
3c	*	*	*	*	*	*	*	*	(*)	(*)	*	*	*
3h	*	*	*	*	(*)	*	*	*	(*)	(*)	*	(*)	*
4	1.8	6.3	4.9	1.6	5.3	*	0.5	(0.6)	0.7	*	*	*	*

[a] An * indicates a transport rate of $\leq 0.3 \times 10^{-6}$ mol/h. Parentheses indicate that a precipitate was observed.

Scheme II. Synthetic Routes to Ethyl 6-(Methoxymethyl)-2-pyridyl Sulfoxide (A) and 2-Bromo-6-((2-tetrahydro-2*H*-pyranyloxy)methyl)pyridine (B)



lanthanide metal cations,[7] the present types of crown ethers formed three-dimensional and stable complexes with hard alkaline earth metal cations as well as heavy and transition metal cations. Further arm functionalization of various crown ethers may, therefore, lead to new and unique cation binding and subsequent chemical functions.[14]

Experimental Section

Materials. 1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane (diaza-18-crown-6), 1,4,7,10,13-pentaoxa-16-azacyclooctadecane (aza-18-crown-6), and 1,4,10,13-tetrathia-7,16-diazacyclooctadecane (thia-analog) were commercially available and used without additional purification. Diaza-18-crown-6s 1a and 1i and 3-(bromomethyl)biphenyl, precursor for crown ether 1j, were synthesized by methods described in the literature.[6,15,16] All new compounds were confirmed as pure materials by TLC analysis and had correct elemental compositions determined by microanalysis and high-resolution mass spectroscopy (EI and FAB modes). Melting points are uncorrected.

Synthesis of Ethyl 6-(Methoxymethyl)-2-pyridyl Sulfoxide (A) (Eq 1 in Scheme II): 2-Bromo-6-(methoxymethyl)-pyridine. To a suspension of NaH (1.01 g, 25.3 mmol, 60% in mineral oil) in THF (40 mL) was added a THF (32 mL) solution of 2-bromo-6-(hydroxymethyl)pyridine (4.0 g, 21.3 mmol) at 0 °C. After the formation of hydrogen gas ceased, iodomethane (4.97 g, 35.0 mmol) was added dropwise to the mixture at the same temperature. It was diluted with EtOAc (200 mL) after 30 min of stirring at room temperature. The whole was washed with water (5 mL × 3) and brine (5 mL) and dried over $MgSO_4$. After solvent was evaporated, residual oil was distilled to give methyl ether (3.66 g) in 85% yield: bp 85–87 °C/1 mmHg; ^1H NMR ($CDCl_3$) δ 3.47 (s, 3H), 4.56 (s, 2H), 7.38 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 58.60, 74.37, 119.63, 126.38, 138.78, 141.06, 159.95. Anal. Calcd for C_7H_8OBrN: C, 41.61; H, 3.99; N, 6.93. Found: C, 41.88; H, 4.00; N, 6.67.

Ethyl 6-(Methoxymethyl)-2-pyridyl Sulfoxide (A). To an ice-cooled suspension of NaH (2.7 g, 67.5 mmol, 60% in mineral oil) in HMPA (30 mL) was added ethanethiol (5 mL, 67.5 mmol) at 0 °C. After the formation of hydrogen gas stopped, 2-bromo-6-(methoxymethyl)pyridine (4.5 g, 22.3 mmol) in HMPA (10 mL) was added, and the mixture was stirred for 30 min at room temperature. Following the addition of water (10 mL), the resulting mixture was extracted with a mixture of ether (200 mL)

(14) Some lanthanide complexes with the bipyridine-armed crown ethers were demonstrated to be effective carriers of hydrophilic amino acid ester salts such as HisOMe·2H⁺ and LysOEt·2H⁺ cations: Tsukube, H.; Uenishi, J.; Higaki, H.; Kikkawa, K. *Chem. Lett.* **1992**, 2307.

(15) Tsukube, H.; Takagi, K.; Higashiyama, T.; Iwachido, T.; Hayama, N. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1033.

(16) (a) Hammond, G. S.; Reeder, C. E. *J. Am. Chem. Soc.* **1958**, *80*, 573. (b) Grovenstein, E.; Wentworth, G. *Ibid.* **1967**, *89*, 2348.

and hexane (200 mL). The extract was washed with water (5 mL × 4) and dried over $MgSO_4$. Solvent was removed under reduced pressure. The crude sulfide was dissolved in MeOH (100 mL) and cooled on an ice bath. MMPP (about 0.5 equiv) was added portionwise until sulfide oxidized completely to sulfoxide by monitoring on TLC. The reaction mixture was filtered, and the filtrate was condensed under reduced pressure. The oily residue was extracted with $CHCl_3$ (300 mL) and washed with water (5 mL × 4). The extract was dried over $MgSO_4$ and evaporated. Residual oil was purified by flash chromatography on silica gel eluted with 50% EtOAc in hexane to give sulfoxide **A** (oil, 3.28 g) in 74% yield: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.3 Hz, 3H), 2.90 (dq, J = 13.6, 7.3 Hz, 1H), 3.17 (dq, J = 13.6, 7.3 Hz, 1H), 3.49 (s, 3H), 4.59 (s, 2H), 7.50 (dd, J = 7.7, 0.7 Hz, 1H), 7.88 (dd, J = 7.7, 0.7 Hz, 1H), 7.94 (t, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 5.25, 47.25, 58.70, 74.67, 118.70, 121.89, 138.07, 158.94, 163.17; IR (film) 1060 cm^{-1}. Anal. Calcd for $C_9H_{13}O_2NS$: C, 54.25; H, 6.58; N, 7.03. Found: C, 54.54; H, 6.65; N, 7.29.

Synthesis of 2-Bromo-6-((2-tetrahydro-2*H*-pyranyloxy)methyl)pyridine (B) (Eq 2 in Scheme II): 2-Bromo-6-(hydroxymethyl)pyridine. To a stirred solution of 2,6-dibromopyridine (3 g, 12.7 mmol) in a mixture of THF (8 mL), ether (16 mL), and hexane (8 mL) was added n-BuLi (12.7 mmol, 7.86 mL, 1.61 M in hexane) drop-by-drop at −78 °C over 5 min. After the mixture was stirred for 5 min, DMF (2.01 mL, 26.3 mmol) was slowly added dropwise to the mixture over 10 min at the same temperature. The reaction mixture was warmed to −50 °C and quenched with MeOH (15 mL). Then, $NaBH_4$ (487 mg, 12.9 mmol) was added at room temperature. After addition of acetone (1.5 mL), the mixture was diluted with EtOAc (300 mL). The whole was washed with water (6 mL × 3) and brine (6 mL) and dried over $MgSO_4$. Solvent was evaporated, and the residue was purified by column chromatography on silica gel eluted with 20% EtOAc in hexane to give an oily product (1.62 g) in 68% yield: mp 32–33 °C; ^{1}H NMR ($CDCl_3$) δ 4.85 (s, 2H), 7.37 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 64.16, 119.30, 126.61, 139.06, 141.32, 161.24; IR (film) 3360 cm^{-1}. Anal. Calcd for C_6H_6OBrN: C, 38.33; H, 3.21; N, 7.45. Found: C, 38.60; H, 3.35; N, 7.27.

2-Bromo-6-((2-tetrahydro-2*H*-pyranyloxy)methyl)pyridine (B). To a mixture of 2-bromo-6-(hydroxymethyl)pyridine (2 g, 10.6 mmol) and 3,4-dihydro-2H-pyran (1.07 g, 12.7 mmol) in CH_2Cl_2 (15 mL) was added *p*-toluenesulfonic acid (607 mg, 23.5 mmol) at 0 °C in several portions. The mixture was stirred for 30 min at room temperature and quenched with aqueous $NaHCO_3$ (10 mL). It was extracted with EtOAc (130 mL) and washed with water (6 mL × 3) and brine (6 mL). The extract was dried over $MgSO_4$ and evaporated. Residual oil was purified by column chromatography on silica gel eluted with 5% EtOAc in hexane to give THF ether **B** (oil, 2.63 g) in 91% yield: ^{1}H NMR ($CDCl_3$) δ 1.50–1.95 (m, 6H), 3.51 (m, 1H), 3.89 (m, 1H), 4.62 (d, J = 6.2 Hz, 1H), 4.86 (d, J = 6.2 Hz, 1H), 4.93 (m, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.23, 25.24, 30.37, 62.17, 68.96, 98.45, 119.85, 126.37, 138.83, 141.13, 160.37; HRMS *m/e* calcd for $C_{11}H_{14}OBrN$ 271.0208, found 271.0234.

Synthesis of 6-(Methoxymethyl)-6′-((2-tetrahydro-2*H*-pyranyloxy)methyl)-2,2′-bipyridine (C) (Step a in Scheme I). To a THF (5 mL) solution of bromopyridine **B** (579 mg, 2.13 mmol) was added n-BuLi (2.25 mmol, 1.4 mL, 1.61 M in hexane) at −78 °C over 5 min. Lithiation was completed in 10 min at the same temperature, and then sulfoxide **A** (300 mg, 1.5 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred for an additional 30 min at the same temperature and for 10 min at room temperature and then quenched with water (15 mL). It was extracted with EtOAc (150 mL), washed with water (5 mL × 3), and dried over $MgSO_4$. After solvent was evaporated, the residue was purified by flash chromatography on silica gel eluted with 5% EtOAc in hexane to give the coupling product **C** (217 mg) in 46% yield: ^{1}H NMR ($CDCl_3$) δ 1.51–1.99 (m, 6H), 3.51 (s, 3H), 3.58 (m, 1H), 3.95 (ddd, J = 11.6, 8.6, 3.3 Hz, 1H), 4.67 (s, 2H), 4.74 (d, J = 13.5 Hz, 1H), 4.83 (t, J = 3.4 Hz, 1H), 4.98 (d, J = 13.5 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.49 (dd, J = 7.7, 0.7 Hz, 1H), 7.81 (td, J = 7.7, 1.5 Hz, 2H), 8.29 (dd, J = 7.7, 1.1 1H), 8.30 (dd, J = 7.7, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.26, 25.35, 30.49, 58.63, 62.08, 69.89, 75.64, 98.29, 119.55, 119.72, 121.00, 121.08, 137.24, 137.29, 155.30, 155.46, 157.80, 158.06. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.79; H, 7.05; N, 8.91. Found: C, 69.06; H, 7.21; N, 8.69.

Synthesis of 6-(Bromomethyl)-6′-(methoxymethyl)-2,2′-bipyridine D (Step b in Scheme I): 6-(Hydroxymethyl)-6′-(methoxymethyl)-2,2′-bipyridine. A mixture of THP ether **C** (217 mg, 0.69 mmol) and HCl (3 drops) in MeOH (3 mL) was stirred for 40 min at room temperature. The reaction mixture was made basic by addition of aqueous NaOH (1 N), condensed under reduced pressure, and extracted with $CHCl_3$ (50 mL). The organic extract was washed with water (3 mL × 2) and dried over $MgSO_4$. Solvent was evaporated, and the residue was purified by column chromatography on silica gel eluted with CH_2Cl_2 to give alcohol (113 mg) in 71% yield: mp 44.0–45.5 °C (benzene/hexane (1:1)); ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 4.14 (bs, 1H), 4.67 (s, 2H), 4.82 (d, J = 0.7 Hz, 2H), 7.23 (dd, J = 7.7, 0.7 Hz, 1H), 7.45 (dd, J = 7.7, 1.1 Hz, 1H), 7.79 (t, J = 7.7 Hz, 1H), 7.83 (t, J = 7.7 Hz, 1H), 8.29 (d, J = 7.7 Hz, 1H), 8.33 (dd, J = 7.7, 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 58.76, 63.91, 75.64, 119.62, 119.82, 120.36, 121.37, 137.47, 137.60, 154.78, 154.85, 158.06, 158.16. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.81; H, 6.06; N, 12.08.

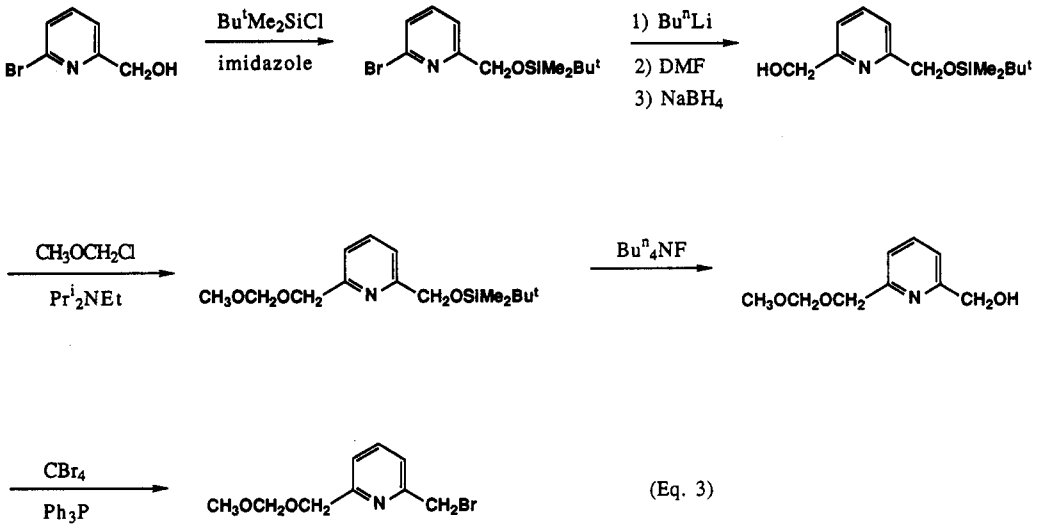
6-(Bromomethyl)-6′-(methoxymethyl)-2,2′-bipyridine. To a mixture of the alcohol prepared above (317 mg, 1.38 mmol) and CBr_4 (736 mg, 2.22 mmol) in CH_2Cl_2 (6 mL) was added triphenylphosphine (427 mg, 1.63 mmol) in several portions at 0 °C. The reaction mixture was stirred for 20 min at the same temperature and then directly passed through silica gel short column chromatography using 10% EtOAc in hexane as an eluent to give the desired bromide **D** (333 mg) in 83% yield: mp 77.0–79.0 °C (benzene/hexane (1:19)); ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 4.62 (s, 2H), 4.66 (s, 2H), 7.45 (dd, J = 7.7, 1.1 Hz, 1H), 7.46 (dd, J = 7.7, 1.1 Hz, 1H), 7.80 (t, J = 7.7 Hz, 1H), 7.83 (t, J = 7.7, 0.9 Hz, 1H), 8.34 (dd, J = 7.7, 0.9 Hz, 1H), 8.35 (d, J = 7.7 Hz, 1H). Anal. Calcd for $C_{13}H_{13}N_2OBr$: C, 53.08; H, 4.45; N, 9.50. Found: C, 53.44; H, 4.68; N, 9.28.

Synthesis of 2-(Bromomethyl)-6-(((methoxymethyl)oxy)methyl)pyridine (Eq 3 in Scheme III): 2-Bromo-6-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine. To a mixture of 2-bromo-6-(hydroxymethyl)pyridine (7.0 g, 37.2 mmol) and imidazole (10.25 g, 150 mmol) in DMF (35 mL) was added Bu^{t}Me$_2$SiCl (6.72 g, 44.6 mmol) in several portions at room temperature. The mixture was stirred for 15 min and extracted with ether (100 mL). The extract was washed with water (5 mL × 3), dried over $MgSO_4$, and concentrated under reduced pressure. Residue was purified by column chromatography on silica gel eluted with 2.5% EtOAc in hexane to give silyl ether (10 g) as an oil in 89% yield: bp 122 °C/2 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 6H), 1.00 (s, 9H), 4.85 (s, 2H), 7.20–7.70 (m, 3H); ^{13}C NMR ($CDCl_3$) δ −5.47, 18.24, 25.81, 65.35, 118.56, 125.88, 138.93, 140.83, 163.10. Anal. Calcd for $C_{12}H_{20}OBrNS$: C, 47.68; H, 6.67; N, 4.63. Found: C, 47.74; H, 6.61; N, 4.92.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-(hydroxymethyl)pyridine. One-pot formylation and reduction for this substrate was done in a same manner described in eq 2 in Scheme II except for the eluent (20% EtOAc in hexane) for column chromatography: bp 105 °C/0.2 mmHg (yield 67%); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6H), 0.86 (s, 9H), 3.83 (s, 1H), 4.64 (s, 2H), 4.73 (s, 2H), 7.00 (d, J = 7.7 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.37, 18.36, 25.89, 63.81, 65.85, 118.46, 118.52, 137.32, 157.64, 160.28; IR (film) 3380 cm^{-1}; HRMS *m/e* calcd for $C_{13}H_{23}O_2NSi$ 253.1498, found 253.1499.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-(((methoxymethyl)oxy)methyl)pyridine. To an ice-cooled solution of the protected (hydroxymethyl)pyridine (2.20 g, 8.68 mmol) and diisopropylethylamine (4.49 g, 34.7 mmol) in a mixture of DMF (20 mL) and CH_2Cl_2 (20 mL) was slowly added chloromethyl methyl ether (1.40 g, 17.4 mmol) drop-by-drop. The mixture was stirred for 2 h at room temperature and then diluted with EtOAc (300 mL) and washed with water (9 mL × 3) and brine (9 mL). The extract was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel eluted with 10% EtOAc in hexane to give the ether (1.94 g) in 75% yield: oil; ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6H), 0.95 (s, 9H), 3.41 (s, 3H), 4.68 (s, 2H), 4.77 (s, 2H), 4.83 (s, 2H), 7.29 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.72 (t, J = 7.7 Hz, 1H); ^{13}C

Scheme III. Synthesis of 2-(Bromomethyl)-6-(((methoxymethyl)oxy)methyl)pyridine



(Eq. 3)

NMR ($CDCl_3$) δ -5.4, 18.31, 25.86, 55.41, 65.97, 70.16, 96.27, 118.57, 119.52, 137.22, 156.82, 160.92. Anal. Calcd for $C_{15}H_{27}O_3NSi$: C, 60.57; H, 9.15; N, 4.71. Found: C, 60.71; H, 8.89; N, 5.00.

2-(((Methoxymethyl)oxy)methyl)-6-(hydroxymethyl)pyridine. To a THF (15 mL) solution of the silyl ether (1.85 g, 6.22 mmol) was added tetrabutylammonium fluoride (6.49 mL, 1 M THF solution) at room temperature, and the mixture was stirred for 40 min. It was extracted with EtOAc (200 mL) and washed with water (6 mL × 3) and brine (6 mL). The extract was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with 50% EtOAc in hexane to give alcohol (863 mg) in 76% yield: oil; ^1H NMR ($CDCl_3$) δ 3.39 (s, 3H), 4.20 (b, 1H), 4.68 (s, 2H), 4.71 (s, 2H), 4.75 (s, 2H), 7.16 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.39, 63.95, 69.85, 96.18, 119.12, 119.84, 137.26, 157.00, 158.63; IR (film) 3370 cm^{-1}; HRMS m/e calcd for $C_9H_{13}NO_3$ 183.0896, found 183.0886.

2-(Bromomethyl)-6-(((methoxymethyl)oxy)methyl)pyridine. Bromination was carried out in the manner described in step b in Scheme I except for the eluent for column chromatography, in which 30% EtOAc in hexane was used to give the bromide in 93% yield: oil; ^1H NMR ($CDCl_3$) δ 3.42 (s, 3H), 4.55 (s, 2H), 4.72 (s, 2H), 4.97 (s, 2H), 7.37 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 33.70, 55.47, 69.95, 96.32, 120.61, 122.13, 137.61, 156.19, 158.16. Anal. Calcd for $C_9H_{12}BrNO_2$: C, 43.92; H, 4.91; N, 5.69. Found: C, 44.15; H, 4.97; N, 5.99.

Other (bromomethyl)oligopyridine derivatives were similarly synthesized *via* ipso-substitution.[4,8]

General Coupling Reaction of Aza-18-crown-6 and Side Arm Part (Step c in Scheme I). A mixture of bromide (2.64 mmol), diaza-18-crown-6 (1.26 mmol), and *N,N*-diisopropylethylamine (12.6 mmol) was refluxed in EtOH (10 mL) for 1–2 h. After cooling, solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$ (350 mL), washed with water (3 mL × 3), and dried over $MgSO_4$. $CHCl_3$ was evaporated, and the residue was purified by column chromatography on alumina using 1–5% triethylamine in EtOAc as an eluent to give N,N'-disubstituted diaza-18-crown-6 derivative. N-Substituted aza-18-crown-6 derivatives were similarly prepared.

***N,N'*-Bis((6-(((methoxymethyl)oxy)methyl)-2-pyridyl)methyl)diaza-18-crown-6 (1b):** yield 94%; mp 68–69 °C (CH_2Cl_2/ether (3:2)); ^1H NMR ($CDCl_3$) δ 2.87 (t, J = 5.5 Hz, 8H), 3.42 (s, 6H), 3.60 (s, 8H), 3.83 (t, J = 5.5 Hz, 8H), 3.85 (s, 4H), 4.70 (s, 4H), 4.78 (s, 4H), 7.27 (d, J = 7.7 Hz, 2H), 7.47 (d, J = 7.7 Hz, 2H), 7.65 (t, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.12, 55.38, 61.51, 69.78, 70.24, 70.64, 96.22, 119.39, 121.43, 136.90, 157.06, 159.77; HRMS m/e calcd for $C_{30}H_{48}N_4O_8$ 592.3469, found 592.3481.

***N,N'*-Bis((2,2'-bipyridin-6-yl)methyl)diaza-18-crown-6 (1c):** yield 95%; mp 85–86 °C (CH_2Cl_2/ether (1:1)); ^1H NMR ($CDCl_3$) δ 2.94 (t, J = 5.7 Hz, 8H), 3.63 (s, 8H), 3.68 (t, J = 5.7 Hz, 8H), 3.96 (s, 4H), 7.28 (ddd, J = 6.1, 4.8, 1.3 Hz, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.77 (d, J = 7.7 Hz, 2H), 7.80 (td, J = 7.7, 1.8 Hz, 2H), 8.22 (dd, J = 7.7, 0.7 Hz, 2H), 8.41 (dt, J = 8.1, 1.1 Hz, 2H), 8.66 (dm, J = 4.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.09, 61.39, 69.75, 70.48, 118.87, 120.88, 122.71, 123.27, 136.55, 136.97, 148.44, 154.93, 156.13, 159.45. Anal. Calcd for $C_{34}H_{42}N_6O_4$: C, 68.21; H, 7.07; N, 14.04. Found: C, 68.27; H, 7.00; N, 13.94.

***N,N'*-Bis((6-(2'-pyrazyl)-2-pyridyl)methyl)diaza-18-crown-6 (1d):** yield 76%; mp 106–107 °C (CH_2Cl_2/ether (1:1)); ^1H NMR ($CDCl_3$) δ 2.96 (s, 8H), 3.64 (s, 8H), 3.70 (s, 8H), 3.99 (s, 4H), 7.63 (d, J = 7.7 Hz, 2H), 7.80 (t, J = 7.9 Hz, 2H), 8.19 (d, J = 7.7 Hz, 2H), 8.58 (d, J = 2.2 Hz, 2H), 8.60 (dd, J = 2.6, 1.6 Hz, 2H), 9.63 (d, J = 1.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.28, 61.19, 69.86, 70.71, 119.51, 123.77, 137.39, 143.43, 143.47, 144.21, 151.32, 153.18, 160.08; HRMS m/e calcd for $C_{32}H_{40}N_8O_4$ 600.3170, found 600.3172.

***N,N'*-Bis((2,2'-bipyridin-5-yl)methyl)diaza-18-crown-6 (1e):** yield 53%; mp 112–113 °C (CH_2Cl_2/ether (1:1)); ^1H NMR ($CDCl_3$) δ 2.86 (t, J = 5.9 Hz, 8H), 3.61 (s, 8H), 3.64 (t, J = 5.7 Hz, 8H), 3.78 (s, 4H), 7.28 (ddd, J = 5.9, 4.6, 1.1 Hz, 2H), 7.80 (td, J = 7.7, 1.5 Hz, 2H), 7.84 (dd, J = 8.3, 1.9 Hz, 2H), 8.34 (d, J = 8.1 Hz, 2H), 8.37 (d, J = 8.1 Hz, 2H), 8.62 (d, J = 2.2 Hz, 2H), 8.67 (dm, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 53.85, 57.08, 69.98, 70.72, 120.70, 120.96, 123.50, 135.31, 136.87, 137.53, 149.13, 149.61, 154.98, 156.17. Anal. Calcd for $C_{34}H_{42}N_6O_4$: C, 68.21; H, 7.07; N, 14.04. Found: C, 68.16; H, 6.97; N, 13.76.

***N,N'*-Bis((6-(2'-quinoyl)-2-pyridyl)methyl)diaza-18-crown-6 (1f):** yield 63%; mp 166–168 °C (CH_2Cl_2/ether (1:1)); ^1H NMR ($CDCl_3$) δ 2.97 (t, J = 5.9 Hz, 8H), 3.64 (s, 8H), 3.70 (t, J = 5.9 Hz, 8H), 4.00 (s, 4H), 7.54 (ddd, J = 8.1, 7.0, 1.1 Hz, 2H), 7.61 (d, J = 7.7 Hz, 2H), 7.72 (ddd, J = 8.4, 7.0, 1.5 Hz, 2H), 7.82 (t, J = 7.7 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H), 8.49 (dd, J = 7.9, 0.4 Hz, 2H), 8.58 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.35, 61.58, 69.69, 70.71, 119.09, 119.85, 123.28, 126.55, 127.53, 128.15, 129.39, 129.73, 136.59. 137.22, 147.86, 155.34, 156.40, 159.57. Anal. Calcd for $C_{42}H_{46}N_6O_4$: C, 72.18; H, 6.63; N, 12.02. Found: C, 72.26; H, 6.47; N, 11.73.

***N,N'*-Bis((6'-(methoxymethyl)-2,2'-bipyridin-6-yl)methyl)diaza-18-crown-6 (1g):** yield 75%; mp 140–141 °C (CH_2Cl_2/ether (1:1)); ^1H NMR ($CDCl_3$) δ 2.97 (s, 8H), 3.51 (s, 6H), 3.62 (s, 8H), 3.66 (s, 4H), 3.70 (s, 8H), 3.99 (s, 4H), 7.43 (d, J = 7.7 Hz, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.76 (t, J = 7.7 Hz, 2H), 7.81 (t, J = 7.7 Hz, 2H), 8.25 (d, J = 7.7 Hz, 2H), 8.30 (d, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.30, 58.73, 61.54, 69.92, 70.68, 75.73, 119.27, 119.76, 120.98, 122.95, 137.16, 137.38, 155.23, 155.76, 157.86, 159.49. Anal. Calcd for $C_{38}H_{50}N_6O_6$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.18; H, 7.42; N, 11.99.

***N,N'*-Bis((2,2':6',2''-terpyridin-6-yl)methyl)diaza-18-crown-6 (1h):** yield 74%; mp 149–151 °C (CH_2Cl_2/ether (1:1)); ^1H NMR ($CDCl_3$) δ 2.96 (t, J = 5.9 Hz, 8H), 3.64 (s, 8H), 3.70 (t, J = 5.7 Hz, 8H), 3.98 (s, 4H), 7.32 (ddd, J = 6.6, 5.0, 1.3 Hz, 2H), 7.57 (d, J = 7.7 Hz, 2H), 7.80 (t, J = 7.7 Hz, 2H), 7.85 (td, J = 7.7, 1.8 Hz, 2H), 7.93 (t, J = 7.9 Hz, 2H), 8.42 (dd, J = 7.9, 0.9 Hz, 2H), 8.45 (d, J = 7.3 Hz, 2H), 8.46 (dd, J = 7.7, 0.7 Hz, 2H),

8.61 (d, J = 8.1 Hz, 2H), 8.69 (dm, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.30, 61.49, 69.88, 70.67, 119.15, 120.71, 120.98, 121.09, 123.02, 123.62, 136.71, 137.10, 137.72, 140.01, 155.17, 155.20, 155.52, 156.21, 159.42. Anal. Calcd for $C_{44}H_{48}N_8O_4$: C, 70.19; H, 6.43; N, 16.21. Found: C, 69.91; H, 6.46; N, 14.77.

***N,N'*-Bis((biphenyl-3-yl)methyl)diaza-18-crown-6 (1j)**: yield 98%; mp 84–85 °C (CH_2Cl_2/ether (1:1)); ^{1}H NMR ($CDCl_3$) δ 2.85 (t, J = 5.8 Hz, 8H), 2.61 (s, 8H), 3.64 (t, J = 5.8 Hz, 8H), 3.74 (s, 4H), 7.48–7.83 (m, 12H), 7.55–7.62 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 53.75, 59.95, 69.98, 70.65, 125.66, 127.14, 127.56, 127.78, 128.55, 128.57, 128.65, 140.11, 141.03, 141.20. Anal. Calcd for $C_{38}H_{46}N_2O_4$: C, 76.74; H, 7.79; N, 4.71. Found: C, 77.03; H, 7.87; N, 4.60.

***N*-((2-Pyridyl)methyl)aza-18-crown-6 (2a)**: oil; yield 85%; ^{1}H NMR ($CDCl_3$) δ 2.91 (bs, 4H), 3.59–3.69 (m, 20H), 3.90 (bs, 2H), 7.13 (t, J = 6.1 Hz, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.64 (td, J = 7.6, 1.6 Hz, 1H), 8.50 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 54.52, 61.86, 69.98, 70.51, 70.88, 71.00, 121.81, 123.12, 136.38, 148.91, 160.42; FAB-HRMS (M + H) calcd for $C_{18}H_{31}N_2O_5$ 355.2233, found 355.2261.

***N*-((2,2'-Bipyridin-6-yl)methyl)aza-18-crown-6 (2c)**: oil; yield 95%; ^{1}H NMR ($CDCl_3$) δ 2.92 (bs, 4H), 3.63–3.72 (m, 20H), 3.96 (s, 2H), 7.29 (ddd, J = 7.3, 4.8 and 1.1 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.80 (td, J = 8.1 and 1.8 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 8.41 (d, J = 7.7 Hz, 1H), 8.67 (ddd, J = 4.8, 1.8 and 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 54.17, 61.47, 69.70, 70.17, 70.52, 70.66, 118.85, 120.91, 122.77, 123.27, 136.57, 136.99, 148.86, 154.92, 156.19, 159.53; FAB-HRMS (M + H) calcd for $C_{23}H_{34}N_3O_5$ 432.2499, found 432.2486.

***N*-((2,2':6',2''-Terpyridin-6-yl)methyl)aza-18-crown-6 (2h)**: oil; yield 74%; ^{1}H NMR ($CDCl_3$) δ 2.84 (t, J = 5.8 Hz, 4H), 3.54–3.63 (m, 20H), 3.89 (s, 2H), 7.22 (ddd, J = 7.5, 4.8 and 1.2 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.75 (td, J = 7.9 and 1.8 Hz, 1H), 7.85 (t, J = 7.9 Hz, 1H), 8.26–8.40 (m, 3H), 8.53 (dt, J = 7.9 and 1.0 Hz, 1H), 8.60 (ddd, J = 4.7, 1.8 and 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 54.10, 61.45, 69.68, 70.15, 70.52, 70.55, 70.65, 118.90, 120.50, 120.80, 120.89, 122.82, 123.48, 136.59, 136.91, 137.55, 148.84, 154.93, 154.98, 155.35, 155.99, 159.43; FAB-HRMS (M + H) calcd for $C_{28}H_{37}N_4O_5$ 509.2764, found 509.2670.

***N*-Benzylaza-18-crown-6 (2i)**: oil; yield 90%; ^{1}H NMR ($CDCl_3$) δ 2.79 (t, J = 5.9 Hz, 4H), 3.61–3.68 (m, 22H), 7.20–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 53.80, 60.01, 69.91, 70.33, 70.73, 70.82, 126.80, 128.11, 128.87, 139.85; FAB-HRMS (M + H) calcd for $C_{19}H_{32}NO_5$ 354.2281, found 354.2293.

7,16-Bis((2,2'-bipyridin-6-yl)methyl)-1,4,10,13-tetrathia-7,16-diazacyclooctadecane (3c): yield 76%; mp 154–155 °C (CH_2Cl_2/hexane (2:1)); ^{1}H NMR ($CDCl_3$) δ 2.75 (d, J = 5.8 Hz, 4H), 2.77 (d, J = 5.1 Hz, 4H), 2.80 (s, 8H), 2.86 (d, J = 5.1 Hz, 4H), 2.88 (d, J = 5.8 Hz, 4H), 3.91 (s, 4H), 7.30 (ddd, J = 5.9, 4.8, 1.1 Hz, 2H), 7.51 (d, J = 7.7 Hz, 2H), 7.80 (t, J = 7.9 Hz, 2H), 7.81 (t, J = 7.9 Hz, 2H), 8.25 (d, J = 7.7 Hz, 2H), 8.38 (d, J = 7.7 Hz, 2H), 8.67 (dm, J = 4.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 30.44, 32.62, 54.10, 60.43, 119.36, 121.08, 122.89, 123.54, 136.80, 137.32, 149.09, 155.30, 156.17, 158.60. Anal. Calcd for $C_{34}H_{42}N_6S_4$: C, 61.60; H, 6.39; N, 12.68. Found: C, 61.37; H, 6.26; N, 12.42.

7,16-Bis((2,2':6',2''-terpyridin-6-yl)methyl)-1,4,10,13-tetrathia-7,16-diazacyclooctadecane (3h): yield 57%, mp 91–93 °C (CH_2Cl_2/hexane (3:1)); ^{1}H NMR ($CDCl_3$) δ 2.77 (d, J = 6.2 Hz, 4H), 2.79 (d, J = 5.1 Hz, 4H), 2.82 (s, 8H), 2.88 (d, J = 5.1 Hz, 4H), 2.89 (d, J = 5.9 Hz, 4H), 3.93 (s, 4H), 7.33 (ddd, J = 6.1, 5.0, 1.3 Hz, 2H), 7.53 (dd, J = 7.7, 0.7 Hz, 2H), 7.84 (t, J = 7.9 Hz, 2H), 7.85 (td, J = 7.7, 1.8 Hz, 2H), 7.95 (t, J = 7.9 Hz, 2H), 8.43 (dd, J = 7.9, 0.9 Hz, 2H), 8.44 (dd, J = 7.7, 1.1 Hz, 2H), 8.48 (dd, J = 7.7, 0.7 Hz, 2H), 8.62 (dt, J = 8.1, 1.1 Hz, 2H), 8.70 (dm, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 30.53, 32.69, 54.19, 60.53, 119.47, 120.87, 121.03, 121.17, 123.00, 123.72, 136.84, 137.31, 137.85, 149.10, 155.29, 155.45, 155.45, 156.21, 158.62; HRMS m/e calcd for $C_{44}H_{48}N_8S_4$: 816.2882, found 816.2941.

***N,N'*-Bis(di(2-pyridyl)methyl)diaza-18-crown-6 (4)**: yield 81%; mp 135–136 °C (CH_2Cl_2/ether (1:1)); ^{1}H NMR ($CDCl_3$) δ 2.91 (t, J = 5.8 Hz, 8H), 3.54 (s, 8H), 3.61 (t, J = 5.8 Hz, 8H), 5.23 (s, 2H), 7.11 (dd, J = 9.2, 4.4 Hz, 4H), 7.62 (d, J = 3.3 Hz, 8H), 8.52 (dt, J = 5.3, 1.4 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 51.06, 69.72, 70.67, 75.19, 122.09, 123.59, 136.39, 149.10, 160.84. Anal. Calcd for $C_{34}H_{42}N_6O_4$: C, 68.21; H, 7.07; N, 14.04. Found: C, 68.32; H, 7.12; N, 13.90.

Extraction Experiment. Extraction experiments were carried out by adding a CH_2Cl_2 solution of crown ether (0.015 mmol/1.5 mL) to an aqueous solution of metal perchlorate (0.015 mmol/1.5 mL). After the mixture had been stirred for 2 h, the aqueous phase was separated. The concentrations of metal cations were determined by atomic absorption or flame spectroscopic method (performed at Exlan Technical Center Co., Okayama).

Transport Experiments. Transport experiments were performed at room temperature (ca. 20 °C) in a U-tube glass cell (2.0-cm i.d.).[17] The carrier, dissolved in CH_2Cl_2, was placed in the base of the U-tube, and two aqueous phases were placed in the tube arms, floating on the membrane phase. The membrane phase was stirred constantly with a magnetic stirrer. The transport rates listed in Table III were calculated from the initial rates of appearance of cotransported ClO_4^- anion into the aq 2 phase, which was determined by a ClO_4^- ion-selective electrode (Orion 93-81). The transported amount of each metal cation was also determined by an atomic absorption or flame spectroscopic method (carried out at Exlan Technical Center Co., Okayama) and was almost equal to that of the cotransported ClO_4^- anion. We confirmed that all metal salts were rarely transported in the absence of carrier (transport rate < 0.3×10^{-6} mol/h).

Acknowledgment. This research was supported in part by a Grant-In-Aid for Science Research on Priority Areas ("Multiplex Organic System" and "Bioinorganic Chemistry") from the Ministry of Education, Science, and Culture, Japan.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of compounds lacking elemental analyses (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) Tsukube, H. In *Liquid Membranes: Chemical Applications*; CRC Press: Boca Raton, 1990; p 27.

Synthesis of Substituted Fluorenones and Substituted 3′,3′-Dichlorospiro[fluorene-9,2′-thiiranes] and Their Reactivities

Warren Chew, Rosemary C. Hynes, and David N. Harpp*

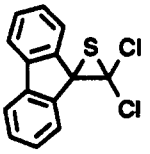
Department of Chemistry, McGill University, Montréal, Québec, Canada H3A 2K6

Received November 11, 1992 (Revised Manuscript Received April 19, 1993)

Several novel 9-fluorenones were synthesized and were used as precursors in an attempt to prepare unique substituted 3′,3′-dichlorospiro[fluorene-9,2′-thiiranes]. Several of the thiiranes were unstable and desulfurized during their preparation (**7a–d**, **11**, **12**). 3′,3′-Dichloro(2,5-dimethoxyspiro[fluorene-9,2′-thiirane] (**7f**) was prepared along with 2,2-dichloro-3,3-bis(4-methoxyphenyl)thiirane (**16**), and 3′,3′-dichloro-10,11-dihydrospiro[5*H*-dibenzo[*a*,*d*]cycloheptane-5,2′-thiirane] (**17**) all of which were stable at room temperature. A study of the reactivity of fluorenyl-substituted thiiranes and other related thiiranes showed that the extent of aromaticity of the substituents at the 3-position of the thiiranes influences their stabilities.

Introduction

As part of our investigation on the mechanism of sulfur extrusion from thiiranes of type **1**,[1] it is necessary to have a general approach to the synthesis of the fluorenones which would serve as precursors to the synthesis of the fluorenyl-substituted thiiranes.



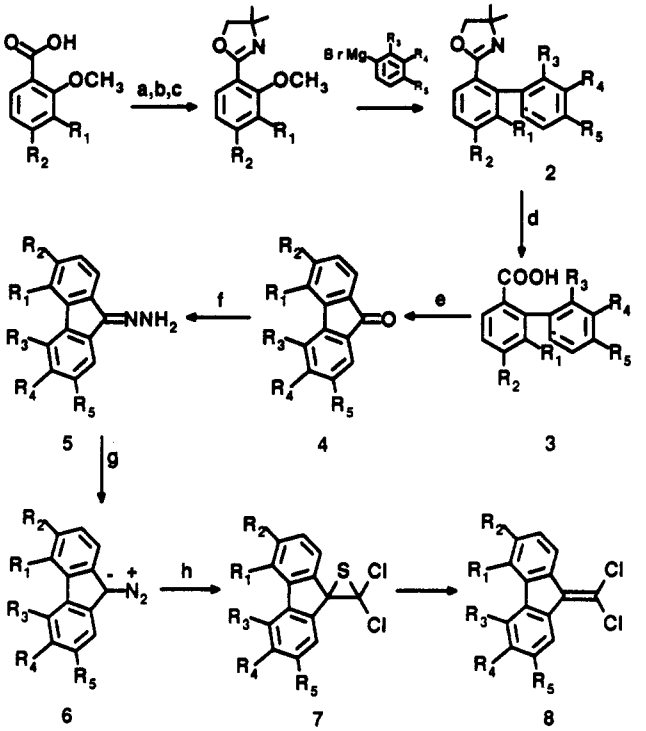
1

Two known methods for the preparation of fluorenones involve intramolecular cyclization steps. The first is a C–C bond formation from a carbonyl to aryl group and the second from aryl to aryl. Another convenient route to substituted fluorenones was recently described by Snieckus and co-workers and involved a remote aromatic metalation strategy.[2] We have successfully utilized the intramolecular cyclization approaches to the synthesis of substituted fluorenones, and we present our results here as well as attempts to prepare thiiranes with various substitution patterns. A study of the reactivity of these thiiranes was also undertaken.

Results and Discussion

The general method employed is outlined in Scheme I. The synthesis of biphenyloxazolines **2** and biphenylcarboxylic acids **3** is based on that described by Meyers.[3] The 2-oxazoline group was suitable protection for the carboxyl function because of its resistance to Grignard reagents used in a subsequent step in the synthesis.[4] The methodology was recently extended in the synthesis of 2-substituted naphthalenes.[5] The deprotection of the oxazoline moiety was accomplished by alkaline hydrolysis, although a milder method for converting oxazolines to carboxylic acids was recently described by Phillion and co-workers in which trifluoromethanesulfonic anhydride was employed followed by alkali saponification.[6]

Scheme I[a]



a: R_2=OCH_3; R_1=R_3=R_4=R_5=H
b: R_2=OCH_3; R_3=CH_3; R_1=R_4=R_5=H
c: R_2=OCH_3; R_5=CH_3; R_1=R_3=R_4=H
d: R_2=R_4=OCH_3; R_1=R_3=R_5=H
e: R_1=R_3=OCH_3; R_2=R_4=R_5=H
f: R_1=R_5=OCH_3; R_2=R_3=R_4=H

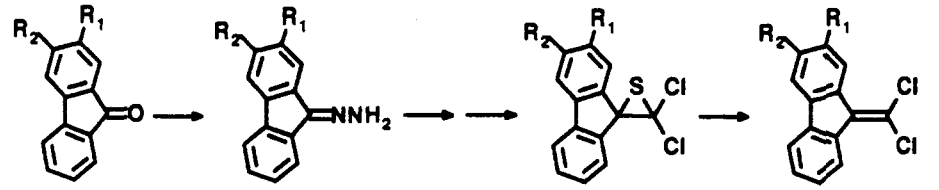
[a] Conditions: (a) $SOCl_2$, 25 °C, 24 h; (b) $NH_2CH_2C(CH_3)_2CH_2OH$, 0 °C; (c) (i) $SOCl_2$; (ii) 20% NaOH; (d) (i) CH_3I, 3 h; (ii) aq NaOH/CH_3OH, reflux 24 h; (e) polyphosphoric acid, 3 h; (f) $NH_2NH_2{\cdot}H_2O$, reflux 24 h; (g) HgO, Na_2SO_4, 10% KOH, 25 °C, 24 h; (h) $CSCl_2$, 0 °C.

With the substituted biphenyls in hand, intramolecular Friedel–Crafts-type acylation was affected by polyphosphoric acid.[7] In the preparation of **4d**, polyphosphoric acid cyclization gave two isomeric compounds, 3,6-

(1) Chew, W.; Harpp, D. N. *Tetrahedron Lett*, **1992**, *33*, 45.
(2) Fu, J.-M.; Zhao, B.-P.; Sharp, M. J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683.
(3) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.
(4) (a) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787. (b) Meyers, A. I.; Meier, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *33*, 853.
(5) Gant, T. C.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010.
(6) Phillion, D. P.; Pratt, J. K. *Synth. Comm.* **1992**, *22*, 13.
(7) (a) Koo, J. *J. Am. Chem. Soc.* **1953**, *75*, 1891. (b) Dupriest, M. T.; Schmidt, C. L.; Kuzmich, D.; Williams, S. B. *J. Org. Chem.* **1986**, *51*, 2021.

0022-3263/93/1958-4398$04.00/0

Scheme II



9 R_1=H; R_2=CH_3 10 11 R_1=H; R_2=CH_3 13 R_2=H; R_2=CH_3

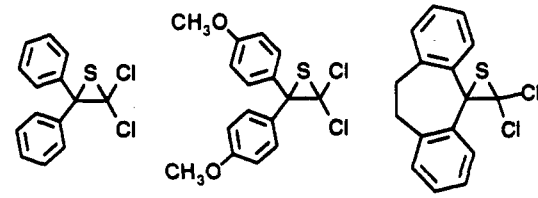
12 R_1=F; R_2=H 14 R_1=F; R_2=H

dimethoxy-9-fluorenone and 1,6-dimethoxy-9-fluorenone, which were easily separated. Conversion of the fluorenones **4** to their hydrazones **5** and then to their diazo derivatives **6** was relatively straightforward following the method described by Baltzly[8] or Schuster.[9] However, under the reaction conditions, fluorenone **4c** could not be converted to its hydrazone.

The diazo derivatives **6** were not isolated but were treated immediately with thiophosgene in situ in an attempt to prepare the fluorenyl-substituted derivatives **7**. The coupling of diazo compounds with thiocarbonyls is one of the easiest methods to prepare thiiranes.[10] This method has been employed with a wide range of both diazo reagents and thioketones and has resulted in a variety of different thiiranes.[11] This route (without isolation of the diazo compound) minimizes generation of azine side products. Azines are known to form readily from diazo compounds[12] and hydrazones.[13] Most of the thiiranes **7** were found to be unstable under the reaction conditions, and they underwent ready desulfurization to their corresponding olefins **8**. Thiirane **7f** was stable long enough to obtain analytical data.

The synthesis of the 3-methylfluorenyl derivative involved C–C bond formation from aryl to aryl. Ring closure was easily effected by Pschorr-type cyclization conditions which have been used to synthesize a variety of substituted fluorenone and azafluorenones.[14] 3-Methylfluorenone (**9**) was obtained which was converted to its hydrazone **10**, oxidized, and then treated with thiophosgene to give thiirane **11**; this thiirane promptly lost sulfur to give the corresponding olefin product **13** (Scheme II). An attempt to prepare the 2-fluorospiro[fluorene-9,2′-thiirane] **12** was also unsuccessful, and only ~1:3 ratio of thiirane to the desulfurized product (**14**) was obtained.

Three other related thiiranes, 2,2-dichloro-3,3-diphenylthiirane (**15**), 2,2-dichloro-3,3-bis(4-methoxyphenyl)-thiirane (**16**), and 3′,3′-dichloro-10,11-dihydrospiro[5*H*-dibenzo[*a*,*d*]cycloheptene-5,2′-thiirane] (**17**) were successfully prepared using the Staudinger methodology.[10] The 3-membered ring heterocycle in **15** and **17** is likely to be more stable than the fluorenyl-substituted compounds because the degree of aromaticity of the phenyl or benzo groups is less than that of the fluorenyl group (*vide infra*).



15 16 17

A substantial mechanistic study which extends our original observations on the mechanism has been carried out.[15] The major thrust of these proposals is consistent with the structure–activity results obtained here. The essential mechanistic pathway is included for clarity (Scheme III). It should be mentioned that we carried out trapping experiments[15,16] in an effort to intercept the cationic intermediate portrayed in Scheme III. These were unsuccessful, indicating that the concatenation of sulfur atoms is a fast process. There is literature precedent for this process.[17]

The study of the general reactivity of substituted derivatives of **1** entailed measuring the possible loss of sulfur when heated in toluene at 80 °C for 45 min. The unsubstituted thiirane **1**, as expected, was transformed entirely to the corresponding olefin under the reaction conditions. Our proposed mechanism has as the rate-determining step (unimolecular path) the ionization of the C–S bond as shown in intermediate **18** (*vide infra*, Scheme IV).[1,15] Therefore, the reaction would be predicted to lose sulfur much faster in the presence of activating groups on the fluorenyl ring system since these substituents would stabilize the developing cation. In the presence of deactivating groups, the dipolar intermediate would be unfavourable and the compound would not be expected to lose sulfur as easily.

The inability to isolate a pure sample of the fluoro-substituted thiirane derivative **12** is consistent with our

(8) Baltzly, R.; Mehta, N. B.; Russell, P. B.; Brooks, R. E.; Grivsky, E. M.; Steinberg, A. M. *J. Org. Chem.* **1961**, *26*, 3669.

(9) Chuang, C.; Lapin, S. C.; Schrock, A. K.; Schuster, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 4238.

(10) (a) Staudinger, H.; Pfenninger, F. *Chem. Ber.* **1916**, *49*, 1941. (b) Staudinger, H.; Siegwart, J. *Helv. Chem. Acta* **1920**, *3*, 833, 840.

(11) (a) Tashiro, M.; Makata, S.; Ischi, S. *Heterocycles* **1979**, *12*, 184. (b) Raasch, M. S. *J. Org. Chem.* **1979**, *44*, 632. (c) L'abbe, G.; Dekerk, J. P.; Martens, C.; Toppet, S. *J. Org. Chem.* **1980**, *45*, 4366. (d) Schaumann, E.; Behr, H.; Adwidjaja, G.; Tangerman, A.; Lammerink, B. H. M.; Zwanenberg, B. *Tetrahedron* **1981**, *37*, 219. (e) Barbaro, G.; Battaglia, A.; Giorgianni, P.; Maccagnani, G.; Macciantelli, D.; Bonini, B. F.; Mazzanti, G.; Zani, P. *J. Chem. Soc., Perkin Trans. 1* **1986**, *381*. (f) Furuhata, T.; Ando, W. *Tetrahedron Letts.* **1987**, *28*, 1179. (g) Rall, K.; Sundermeyer, W. *J. Fluorine Chem.* **1990**, *47*, 121.

(12) (a) Szmant, H. H.; McGinnis, C. *J. Am. Chem. Soc.* **1950**, *72*, 2890. (b) Cohen, S. G.; Cohen, F.; Wang, C. H. *J. Org. Chem.* **1963**, *28*, 1479. (c) Abelt, C. J.; Pleier, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 1795. (d) Sugiyama, M. H.; Celebi, S.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 966.

(13) Kolb, V. M.; Kuffel, A. C.; Spiwek, H. O.; Janota, T. E. *J. Org. Chem.* **1989**, *54*, 2771.

(14) Kyba, E. P.; Liu, S.-T.; Chockalingam, K.; Reddy, B. R. *J. Org. Chem.* **1988**, *53*, 3513.

(15) Chew, W.; Harpp, D. N. *J. Org. Chem.* Following paper in this issue.

(16) Our trapping experiments were similar to those previously carried out: McClelland, R. A.; Mathivanan, N.; Steenken, S. *J. Am. Chem. Soc.* **1990**, *112*, 4857. Cozens, F.; Li, J.; McClelland, R. A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 743.

(17) Davis, R. E. *J. Am. Chem. Soc.* **1958**, *80*, 3565. Steudel, R.; Mausle, J.-J. *Z. Anorg. Allg. Chem.* **1979**, *457*, 165. Harpp, D. N. *Perspectives in the Organic Chemistry of Sulfur*; Zwanenburg, B.; Klunder, A. J. H., Eds.; Elsevier: Amsterdam, 1987; pp 1–22. Steudel, R.; Prenzel, S., *Z. Naturforsch.* **1989**, *44b*, 1499. Williams, C. R.; MacDonald, J. G.; Harpp, D. N.; Steudel, R.; Forster, S. *Sulfur Lett.* **1992**, *13*, 247. Chew, W.; Harpp, D. N.; Steudel, R.; Forster, S. *Sulfur Lett.* **1993**, *15*, 247.