Ligands containing alternating 2,6-linked pyridine and 2,5-linked thiophene units[1]

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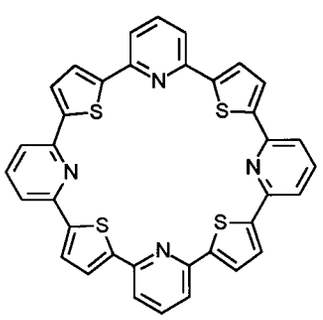
A variety of linear assemblies of alternating pyridine (2,6-linked) [P] and thiophene (2,5-linked) [T] units have been generated with up to seven units and their macrocyclisation investigated. The optimal methods involved the palladium(0) catalysed reaction of thienyl Grignard reagents with bromopyridines. In this way were made TPT, TPTPT, TPTPTPT, BrPTPBr and various $XCH_2PTPTPCH_2X$ derivatives (X = H, Br, OH, OR and SBu-t). Alternative routes whereby pyridine units were 2,6-linked by CH_2SCH_2 units, with the intention of converting the bridge groups into thiophenes by a Hinsberg reaction, were also studied. The latter products {$(HOCH_2[P]CH_2)_2S$ and $(HOCH_2[P]$-$CH_2SCH_2)_2[P]$} proved to be highly effective ligands for transition metals, especially divalent ones such as Co^{2+}, Ni^{2+} and Zn^{2+}. No macrocyclisations were effective.

Introduction

In a foregoing paper[2] we described rapid routes to generate alternating linear assemblies of 2,6-linked pyridine- (P) and 2,5-linked imidazolidin-2-one (I) units and their macrocyclisation to give complexing agents containing two different types of ligand atoms. The primary target of our studies was (c-PIPIPIPI-) containing four alternating units of each heterocycle. This paper describes our endeavours to achieve the synthesis of the comparable system with four pairs of alternating 2,6-pyridyl- and 2,5-thienyl- units **1**. Such a system would have



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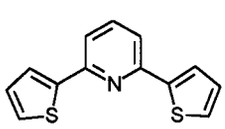

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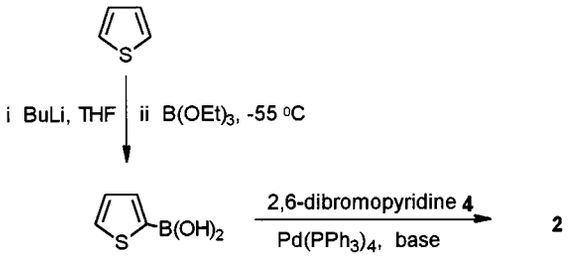
two sets of usefully variable ligand atoms. For example, the pyridine nitrogen can be converted into an *N*-oxide, *N*-amide or quaternary salt while the thiophene can be transformed into its *S*,*S*-dioxide, generating a useful diene which would allow ring conversion of the thiophene into a six-membered analogue by Diels–Alder reaction. Methods for linking such units beyond the 2,6-bis(2-thienyl)pyridine **2** stage are presently unknown, though the vastly improved arsenal (*e.g.* the methods of Suzuki, Stille, palladium(0) catalysed Grignard couplings and other metal-catalysed methods[3]) for the generation of unsymmetrical biaryls from monocyclic precursors should make this task easier. We herein record the successful rapid generation of long linear assemblies of the desired heterocyclic systems, their failure to undergo macrocyclisations, alternative routes *via* thiophene ring acyclic precursors and some aspects of the ligand properties of these systems.

The synthesis of linear alternating assemblies of thiophenes and pyridines

Suzuki coupling. 2,6-Bis(2-thienyl)pyridine (TPT) **2** has been made in poor to moderate yield by three methods: reaction of 2,6-dichloropyridine with 2-thienyllithium gives the desired product in 18% yield,[4] while the nickel chloride–1,3-bis(diphenylphosphonyl)propane-catalysed reaction of 2-thienylmagnesium bromide gives the same product in only 11% yield.[5] However thiophene-2-boronic acid **3**, generated from the lithio-derivative, reacts with 2,6-dibromopyridine **4** under Pd^0 catalysed coupling (the Suzuki reaction) to undergo deboronation and give TPT **2** in 55% yield (the overall yield from thiophene is only 30%).[6] As this product was a key building block in this work, we have carefully examined all aspects of this last reaction and focussed in particular on the deboronation problem. A yield of 78–80% of 2-thienyllithium and thence thiophene-2-boronic acid can be consistently achieved (*cf.* Gronowitz's yield[6] of 50%) by metalation in dry THF followed by slow addition of triethyl borate at −55 °C and careful acidic work-up; the coupling was found to be very sensitive to reactant ratio and more particularly to pH. Using sodium bicarbonate as base, and a 3.5:1 ratio of boronic acid to dibromopyridine ensured a yield >75% in the coupling step, thereby countering the ready deboronation of thiopheneboronic acids in base. However, a more effective solution was to replace the sodium bicarbonate with potassium fluoride,[7] using a two-phase aqueous toluene system, whereby the coupling step proceeded in 90% yield with only a 2.4:1 ratio of acid to pyridine, or 71% yield overall from thiophene (Scheme 1).

Attempts to further utilise Suzuki coupling by generating the boronic acid of **2** by way of metalation-triethyl borate action, followed by KF-catalysed coupling of the acid with 2,6-dibromopyridine gave mostly the starting material TPT **2**. Other methods were therefore sought for the higher oligomers.

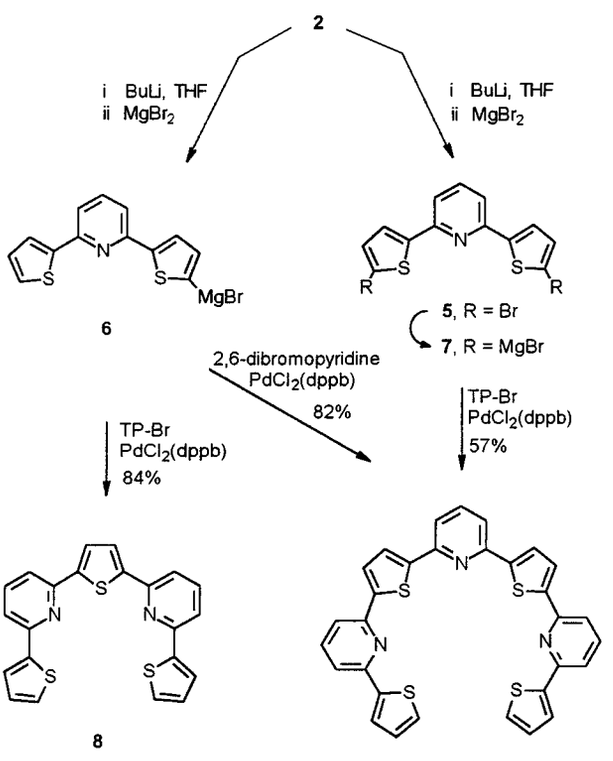
Palladium(0)-catalysed coupling of Grignard reagents. Minato *et al.*[8] have demonstrated the ready coupling of heteroaryl halides and heteroaryl Grignard reagents using $PdCl_2$·$[Ph_3P(CH_2)_4PPh_3]$ as catalyst. Various mixed oligoheteroaryls were made this way, often in good yield, including products containing thiophene and pyridine units. Indeed, coupling of 2-thienylmagnesium bromide with 2,6-dibromopyridine in this way gave TPT **2** in 97% yield. TPT was readily monometalated or dimetalated with butyllithium or converted into the corresponding 2,6-bis(5-bromo-2-thienyl)pyridine (Br-TPT-Br) **5** with *N*-bromosuccinimide in chloroform and acetic acid[9] in 84% yield. The mono- and bis-Grignard derivatives TPT-MgBr **6** and BrMg-TPT-MgBr **7** of TPT were easily formed from the



Base	Ratio 3:4	Yield 2 (%)
$NaHCO_3$	2.4:1	50
	3.0:1	75
	3.5:1	78
KF	2.4:1	90

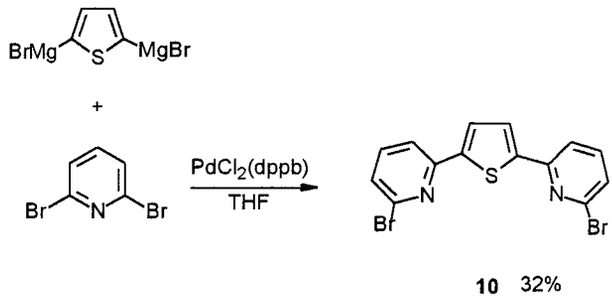
Scheme 1

monolithio and dilithio derivatives using magnesium bromide but the bis-Grignard reagent did not form from Br-TPT-Br **5**. However, thienylmagnesium bromide reacted with an equimolar amount of 2,6-dibromopyridine to give 2-bromo-6-(2-thienyl)pyridine (TP-Br) in 59% yield, the time and temperature of the reaction being critical. This halide was coupled effectively with the mono-Grignard derivative (TPT-MgBr) **6** under Minato conditions to give the pentacycle TPTPT **8** in 84% yield. In a similar manner, TPT-MgBr was coupled with 2,6-dibromopyridine to give the heptacycle TPTPTPT **9** in 82% yield while the same product was isolated in 57% yield from coupling of the bis-Grignard reagent (BrMg-TPT-MgBr) **7** with bromothienylpyridine (TP-Br) (Scheme 2).



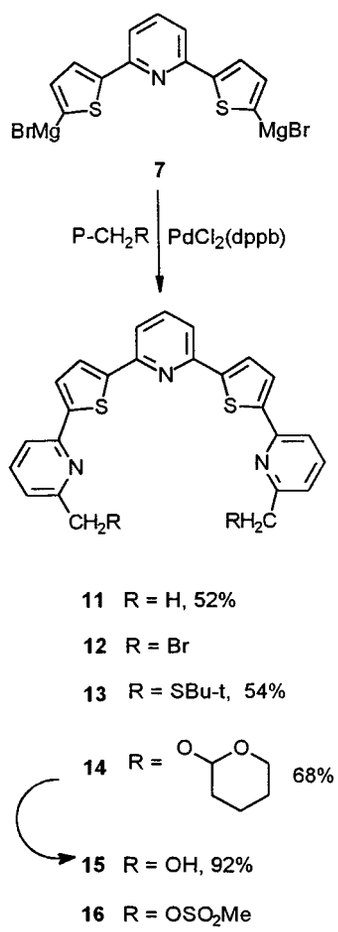
Scheme 2

Oligomers with terminal pyridine units were also required in this work, with a view to coupling two units to give the macrocycle **1**. Moderate yields (32%) of the useful building block (Br-PTP-Br) **10** were made by coupling of equimolar amounts of 2,5-bis(bromomagnesio)thiophene and 2,6-dibromopyridine



Scheme 3

(Scheme 3). The 2,5-bis(bromomagnesio)thiophene was best made indirectly by way of the lithio-derivative since yields of **10** were halved when the Grignard reagent was made directly from 2,5-dibromothiophene. In a similar manner the bis-Grignard reagent (BrMg-TPT-MgBr) **7** was coupled with 2-bromo-6-methylpyridine to yield the pentacyclic product Me-PTPTP-Me **11** in 52% yield, with 2-bromo-6-(*tert*-butylsulfanylmethyl)-pyridine to give **13** in 54% yield and with 2-bromo-6-(tetrahydro-2*H*-pyran-2-yloxymethyl)pyridine to give **14** in 68% yield (Scheme 4).



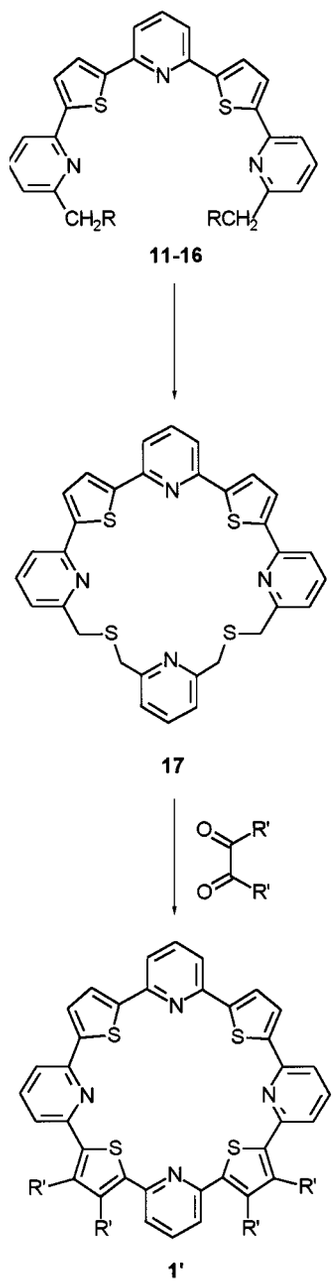
Scheme 4

Macrocyclisation attempts

Armed with a variety of linear precursors, we next sought to cyclise or cycloadd them to form macrocycles such as **1**. The potential of these linear systems to complex with transition metals to produce useful templates gave hope for Minato coupling. Thus, both the penta- (TPTPT) and heptacyclic (TPTPTPT) systems were dimetalated with butyllithium followed by conversion into the corresponding Grignard reagent. Unlike earlier analogous chemistry, the higher oligomers were

only slightly soluble in tetrahydrofuran, making for some serious limitations. The former was then reacted with Br-PTP-Br and the latter with 2,6-dibromopyridine under high dilution Minato conditions. In both cases only starting material and polymeric matter was produced.

We therefore examined the prospect of macrocyclisation of a functionalised pyridine-terminated oligomer, finally forming a thiophene ring from a bis-2-pyridylmethylsulfide unit (-P-CH_2-SCH_2-P-) **17**, utilising the well-known Hinsberg methodology[10] (Scheme 5). To this end, several above-mentioned oligomers

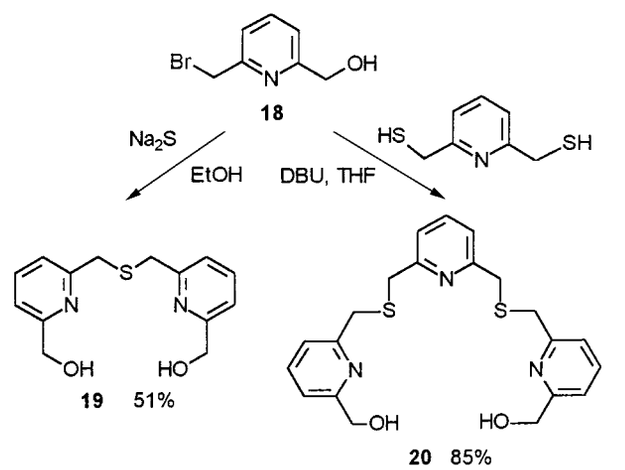


Scheme 5 Proposed Hinsberg approach to macrocycles **1′**.

11–**16** with useful functionalised pyridyl-termini were synthesised and their potential transformation into macrocycles examined. This process required that a pentacyclic precursor **11**–**16** bearing terminal Br, SH or OSO_2Me groups be coupled with a 2,6-bis-functionalised pyridine reagent (RCH_2-P-CH_2R; R = SH, Br or OSO_2Me respectively). The resulting product should then be condensed with a 1,2-dicarbonyl derivative (glyoxal, benzil or dimethyl oxalate) to give the macrocycle.

Such macrocyclisations to the sulfide bridged systems have precedent in the literature. Thus Vögtle,[11] and Martel[12] obtained a mixture of dimeric and trimeric macrocycles by interaction of 2,6-bis(chloromethyl)pyridine with sodium sulfide in low yield. Boekelheide[13] produced high yields of the dimer by interacting the same pyridine with the corresponding bis(sulfanylmethyl)pyridine. A stepwise approach to a tetrameric pyridine-containing bis(sulfanylmethyl)pyridine. A stepwise approach to a tetrameric pyridine-containing sulfide-bridged macrocycle has been made using 2-bromomethyl-6-hydroxymethylpyridine to form a bis-sulfide with 1,3-bis(sulfanylmethyl)benzene followed by mesylation of the hydroxy groups and sodium sulfide mediated cyclisation.[14] Model studies suggested that while 2,6-bis(sulfanylmethyl)-pyridines are unstable and the corresponding bis(bromomethyl) analogues are stable, the reverse is true in the thiophene series. This suggested that the optimal combination should involve the stable precursors. However, we were disappointed to find that although the potentially useful precursors **11**–**13** were easily made, the key derivatives bearing CH_2Br (**12** by bromination of **11**), CH_2SH (by de-*tert*-butylation of **13**) and CH_2-OSO_2Me (**16**, by deprotection of **14** to give the bis-methanol **15** followed by mesylation) were not able to be synthesised.

Another possible Hinsberg approach was also explored whereby 2-bromomethyl-6-hydroxymethylpyridine **18** was transformed into sulfides **19** and **20** by the action of sodium sulfide and 2,6-bis(sulfanylmethyl)pyridine respectively (Scheme 6). These products once again were not able to be converted into



Scheme 6

mesylates, designed to react further with 2,6-bis(sulfanylmethyl)-pyridine to give a macrocycle.

Metal complexation studies

The sulfides **19** and **20** proved to be highly effective ligands for chromium, cobalt, nickel, copper, silver, zinc and silver (and probably other transition metals), giving highly crystalline 1 : 1 complexes with divalent metal chlorides such as Co, Ni and Zn. While most Group 1 and 2 metal picrates were not extracted from aqueous solution by chloroform solutions of these ligands, magnesium and calcium salts were extracted. None of the 'ligands' **2**, **8**, **9**, **11**–**16** showed any extraction capability.

Conclusion

Rapid routes for the assembly of linear alternating 2,6-linked pyridines and 2,5-linked thiophenes have been achieved with up to seven linked groups but their macrocyclisation has so far not been accomplished. An alternative strategy whereby sulfide bridged pyridines could be converted into the desired macrocycle by Hinsberg formation of the thiophene ring was also explored. These precursors, containing two and three pyridine rings proved excellent ligands for divalent transition metals.

Experimental

Melting points were determined on either an Electrothermal capillary instrument or a Reichert Hostage Microscope melting point apparatus and are uncorrected. Infrared spectra were recorded on a UNICAM Research Series 1 FT-IR instrument as liquid films or KBr discs. Ultra-violet spectra were recorded on a UNICAM UV-2 spectrophotometer. Proton NMR spectra were recorded on a JEOL GSX270 MHz FT NMR spectrophotometer at 270 MHz. Chemical shifts are quoted to higher frequency of $SiMe_4$ as internal standard and are given in ppm, with coupling constants, *J*, in Hz. NMR spectra in DMSO-d_6 were obtained at 35 °C and in other solvents at ambient temperature, unless otherwise stated. In NMR data, py refers to the pyridine ring protons and th to the thiophene ring protons. Elemental analyses and high resolution mass spectra were conducted at Newcastle University on a Carlo Erba 1106 Elemental Analyser and a Kratos MS80RF mass spectrometer respectively. Silica gel TLC was performed on E. Merck plastic plates coated with 0.2 mm silica 60 F_{254}. Flash chromatography was performed with Janssen or E. Merck silica gel, particle size 35–70 mm.

Commercial reagents were normally used without further purification. For air sensitive reactions, solid reagents were dried over phosphorus pentoxide (P_2O_5) in a dessicator under reduced pressure for one day prior to use, liquid reagents were dried and distilled according to standard methods.[15] Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Chloroform and dichloromethane were distilled from calcium hydride and stored over 3 Å molecular sieves. Methanol and ethanol were distilled from Mg–I_2 and stored over 3 Å molecular sieves. Toluene and benzene were distilled from calcium hydride and stored over 4 Å molecular sieves. Ether implies diethyl ether. Reactions requiring anhydrous conditions were performed in oven-dried apparatus under nitrogen. Light petroleum refers to bp 60–80 °C.

The following compounds were made by literature methods: dimethyl pyridine-2,6-dicarboxylate,[16] 2,6-bis(hydroxymethyl)-pyridine,[17] 2,6-bis(bromomethyl)pyridine,[18] 2-bromomethyl-6-hydroxymethylpyridine,[18] 2,6-bis(sulfanylmethyl)pyridine,[19] 2-bromo-6-methylpyridine,[20] 2-bromo-6-bromomethylpyridine,[21] 2-(*tert*-butylsulfanylmethyl)pyridine,[22] 2-bromopyridine-6-carbaldehyde,[23] 2-bromo-6-(1,3-dioxolan-2-yl)pyridine,[23] 2-bromo-6-(tetrahydro-2*H*-pyran-2-yloxymethyl)pyridine[24] and 2-bromo-6-methyloxymethylpyridine.[24]

Dichloro[1,4-bis(diphenylphosphino)butane]palladium Pd(dppb)Cl_2[25]

To a mixture of palladium chloride (1.0 g, 5.64 mmol) dissolved in MeOH (40 mL) under nitrogen was added 1,4-bis(diphenylphosphino)butane (2.405 g, 5.64 mmol). The solution was heated at reflux for 1 h to form an insoluble product. The reaction mixture was cooled to room temperature and the solid separated by filtration, washed with MeOH (20 mL) and air dried to give dichloro[1,4-bis(diphenylphosphino)butane]palladium as a brown solid (3.18 g, 94%).

Thiophene-2-boronic acid 3[26]

To a stirred mixture of thiophene (20.0 g, 0.24 mol) in dry THF (150 mL) at −40 °C under nitrogen was slowly added n-butyllithium (145 mL, 1.64 mmol ml^{-1}, 0.24 mol). The reaction mixture was stirred for 30 min and then slowly warmed to −10 °C for another 30 min. This solution was then cooled to −50 °C and trimethyl borate (88 g, 0.85 mol) was added over 1 h. After a further 30 min at −55 °C, the solution was slowly warmed to room temperature, and then was neutralised with HCl (150 mL, 2 M). Ether (100 mL) was added to the solution, and the ether layer was extracted with aqueous NaOH three times (3 × 100 mL, 3 M). The aqueous layer was acidified at 0–10 °C with HCl (35%) to pH 1 and then extracted with ether (3 × 100 mL). The combined ether layer was evaporated under reduced pressure to give thiophene-2-boronic acid **3** as a waxy white solid (37.4 g, 79%, containing ~30% water).

2,6-Bis(2-thienyl)pyridine (TPT) 2[6]

(1) Coupling with sodium bicarbonate as base. To a stirred mixture of 2,6-dibromopyridine (5.00 g, 0.02 mol) and tetrakis(triphenylphosphine)palladium(0) (1.00 g, 0.86 mmol) in 1,2-dimethoxyethane (150 mL) was added thiophene-2-boronic acid (11.1 g, wet 70%, 0.06 mol), immediately followed by sodium bicarbonate solution (130 mL, 1 M). The reaction mixture was heated at reflux for 4 h, with vigorous stirring under nitrogen. After cooling, traces of the insoluble catalyst were filtered off at room temperature, the organic layer was evaporated under reduced pressure, and water (150 mL) was added to the residue. The aqueous layer was extracted with ether (3 × 100 mL) and the combined ethereal phase was washed with water (100 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography using 30% ethyl acetate–70% light petroleum to give 2,6-bis(2-thienyl)pyridine **2** as pale yellow crystals (4.32 g, 75%), mp 78.5–79.7 °C (lit.,[6] mp 78–80 °C); $\delta_H(CDCl_3)$: 7.65 (t, 1H, *J* 7.4, py 4-H), 7.62 (dd, 2H, *J* 4.0, 1.1, th 3-H), 7.43 (d, 2H, *J* 7.4, py 3- and 5-H), 7.40 (dd, 2H, *J* 5.1, 1.1, th 5-H), 7.10 (dd, 2H, *J* 5.1, 4.0, th 4-H).

(2) Coupling with potassium fluoride as base. A mixture of 2,6-dibromopyridine (1.0 g, 4.22 mmol), tetrakis(triphenylphospine)palladium(0) (0.175 g, 0.15 mmol), thiophene-2-boronic acid (1.86 g, wet 70%, 10.13 mmol, 20% excess) and powdered potassium fluoride (0.5 g, 8.6 mmol) in toluene (30 mL) and water (30 mL) was heated at relux for 4 h, with vigorous stirring under nitrogen. After the above work-up 2,6-bis(2-thienyl)pyridine **2** (0.91 g, 90%) was obtained as pale yellow crystals, mp 78–79 °C.

(3) Grignard coupling. To a stirred mixture of magnesium turnings (3.72 g, 0.153 mol) in dry THF (50 mL) was slowly added 2-bromothiophene (24.97 g, 0.153 mol) in dry THF (60 mL) during 45 min. The Grignard reaction was initiated by gentle warming and the mixture was stirred for 3.5 h at room temperature under nitrogen, and then heated at reflux for 15 min. After all the magnesium turnings had disappeared, this solution was cooled to 0–5 °C in an ice bath, and then was slowly transferred into a stirred mixture of 2,6-dibromopyridine (16.30 g, 0.067 mol) and $PdCl_2$(dppb) (0.7 g, 1.16 mmol) in dry THF (30 mL) at room temperature. The reaction mixture was heated at reflux for 4 h under nitrogen, cooled to room temperature, most of the solvent removed and diethyl ether (150 mL) added. The organic phase was washed with saturated ammonium chloride solution (150 mL) and then water (150 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography as before to give 2,6-bis(2-thienyl)pyridine as pale yellow crystals (16.3 g, 97%), mp 78–79 °C.

Attempted synthesis of TPT boronic acid

To a stirred mixture of TPT (1.0 g, 4.11 mmol) in dry THF (20 mL) at −40 °C under nitrogen was slowly added n-butyllithium (2.5 mL, 1.64 mmol ml^{-1}, 4.10 mmol). The reaction mixture was stirred for 30 min and then was slowly warmed to −10 °C for another 30 min. This solution was then cooled to −50 °C and trimethyl borate (1.5 g, 14.4 mmol) in THF (10 mL) was added over 30 min. After a further 30 min at −55 °C, the solution was slowly warmed to room temperature, and then was neutralised with HCl (2 M). Ether (40 mL) was added to the solution, and the ether layer was extracted with NaOH (3 M, 3 × 40 mL). The aqueous layer was acidified at 0–10 °C with conc. HCl to pH 1

and then extracted with ether (3 × 40 mL). The combined ether layer was evaporated to give a mixture containing starting material. Attempts to separate the residue by chromatography failed but ^{1}H NMR spectroscopy of the crude product showed a mixture. Without further purification, the crude TPT boronic acid was reacted with 2,6-dibromopyridine using the organoboron coupling reaction conditions described above (sodium bicarbonate solution as base). After work-up, only starting material TPT was obtained.

Attempted synthesis of TPT using silanes

A mixture of 2-trimethylsilylthiophene (1.00 g, 6.4 mmol), 2,6-difluoropyridine (0.29 g, 2.5 mmol) and caesium fluoride (0.1 g, 0.65 mmol) in dry DMF (20 mL) was heated at 110 °C under nitrogen. After 12 h TLC showed starting material 2,6-difluoropyridine and no formation of TPT. The reaction temperature was raised to 120 °C for a further 24 h. TLC still showed no formation of TPT.

2,6-Bis(5-bromo-2-thienyl)pyridine (BrTPTBr) 5

To a stirred mixture of 2,6-bis(2-thienyl)pyridine (TPT) (8.00 g, 0.0328 mol) in chloroform (20 mL) and acetic acid (20 mL) was slowly added NBS (13.0 g, 0.073 mol) in chloroform (20 mL) and acetic acid (20 mL) in half an hour, the mixture was stirred for 2 h at room temperature, and then was heated at reflux for 0.5 h. After the solution was cooled to room temperature, the white precipitates were filtered off. Dichloromethane (20 mL) was added to the solution. The organic layer was washed with NaOH solution (50 mL, 2 M) then water (50 mL) and dried over magnesium sulfate. After evaporation, the white residue was recrystallised from a chloroform–methanol solution to give *2,6-bis(5-bromo-2-thienyl)pyridine* (BrTPTBr) **5** as white crystals (11.09 g, 84%), mp 210.5–211.5 °C (Found: C, 38.8; H, 1.7; N, 3.5. $C_{13}H_7Br_2NS_2$ requires C, 38.9; H, 1.8; N, 3.5%); $\delta_H(CDCl_3)$: 7.24 (d, 2H, *J* 4.9, th 4-H), 7.59 (d, 2H, *J* 4.9, th 3-H), 7.70 (d, 2H, *J* 7.6, py 3- and 5-H), 7.87 (t, 1H, *J* 7.6, py 4-H); ν_{max}(KBr/cm^{-1}) 2360, 2340, 1584, 1560, 1457, 1439, 1274, 1164, 986, 784, 661.

Attempted synthesis of mono-α-brominated-TPT (TPTBr)

To a stirred mixture of TPT (0.1427 g, 0.586 mmol) in chloroform (2 mL) and acetic acid (2 mL) was slowly added NBS (0.1044 g, 0.586 mmol) in chloroform (5 mL) and acetic acid (5 mL) over half an hour and the mixture was then stirred for 2 h at room temperature. Dichloromethane (10 mL) was added. The organic layer was washed with NaOH solution (2 M, 10 mL) and then water (10 mL) and dried over magnesium sulfate. After evaporation, the crude product (0.200 g) was checked by TLC. It contained three very close-eluting spots. Attempted separation of these three compounds by column chromatography proved ineffective.

Attempted synthesis of bis-Grignard reagent 7 of TPT 2 from BrTPTBr 5

A mixture of magnesium (0.061 g, 2.50 mmol), BrTPTBr **5** (0.5 g, 1.243 mmol) and a crystal of iodine in dry tetrahydrofuran (20 mL) under nitrogen was stirred at room temperature for 3 h and then was heated at reflux for 24 h. No disappearance of magnesium turnings was observed. TLC only showed starting material BrTPTBr.

2-Bromo-6-(2-thienyl)pyridine (TPBr)

To a stirred mixture of magnesium turnings (1.607 g, 0.066 mol) in dry tetrahydrofuran (100 mL) was added 2-bromothiophene (10 g, 0.060 mol) in dry THF (50 mL) over 45 min, the Grignard reaction being initiated by gently warming. The mixture was stirred for 3.5 h at room temperature under nitrogen and then was heated at reflux for 15 min. This solution was cooled to 0–5 °C and transferred to a stirred mixture of 2,6-dibromopyridine (13.08 g, 0.055 mol) and $PdCl_2$(dppb) (0.5 g, 0.828 mmol) in dry THF (100 mL). The mixture was stirred at room temperature for a further 5 h. Most of the solvent was removed and ether (150 mL) was added. The organic layer was washed with saturated ammonium chloride solution (150 mL) and then water (150 mL) and dried over magnesium sulfate. After evaporation, the crude liquid product was distilled at 125 °C (1 mmHg) to give 2-bromo-6-(2-thienyl)pyridine as a colourless liquid (8.5 g, 59%). MS (EI, *m*/*z*) 239, 241 (Found: 239.2410. C_9H_6BrNS requires 239.2410); $\delta_H(CDCl_3)$: 7.02 (dd, 1H, *J* 4.8, 4.4, th 4-H), 7.20 (d, 1H, *J* 7.3, py 3-H), 7.34 (dd, 1H, *J* 4.8, 0.8, th 5-H), 7.40 (d, 1H, *J* 7.6, py 5-H), 7.42 (dd, 1H, *J* 7.3, 7.6, py 4-H), 7.51 (dd, 1H, *J* 4.4, 0.8, th 3-H); ν_{max}(KBr/cm^{-1}) 1574, 1548, 1530, 1440, 1416, 1398, 1160, 1121, 991, 786, 745, 706.

2,5-Bis[2-(2-thienyl)-6-pyridyl]thiophene TPTPT 8

To a stirred mixture of magnesium turnings (0.165 g, 6.78 mmol) in dry THF (20 mL) under nitrogen was added dropwise 1,2-dibromoethane (1.27 g, 6.76 mmol) in dry THF (10 mL). The reaction was initiated by gently warming and the mixture was heated at reflux for 50 min and then cooled to 0 °C. In a separate flask, to a stirred mixture of TPT (1.5 g, 6.16 mmol) in dry THF (20 mL) at −40 °C under nitrogen, was added slowly n-butyllithium (3.76 mL, 1.64 mmol ml^{-1}, 6.16 mmol), the mixture was stirred for 30 min at −40 °C and then slowly warmed to room temperature for 30 min. This solution was cooled to −60 °C and the above $MgBr_2$ solution was added slowly. After a further 30 min at −60 °C, the solution was warmed slowly to ambient temperature to give the Grignard reagent **6**. To this Grignard reagent solution was added a solution of 2-bromo-6-(2-thienyl)pyridine (1.48 g, 6.16 mmol) and $PdCl_2$(dppb) (0.15 g, 0.248 mmol) in dry tetrahydrofuran (10 mL) and the mixture was heated at reflux under nitrogen for 4 h. Most of the solvent was removed under reduced pressure and dichloromethane (100 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride (100 mL) and then water (100 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography (dichloromethane–light petroleum, 1:1) and then recrystallised from chloroform–light petroleum to give *TPTPT* **8** as pale yellow crystals (2.09 g, 84%), mp 207–208 °C (Found: C, 65.5; H, 3.4; N, 6.9. $C_{22}H_{14}N_2S_3$ requires C, 65.6; H, 3.5; N, 7.0%); $\delta_H(CDCl_3)$: 7.14 (dd, 2H, *J* 4.7, 4.2, terminal th 4-H's), 7.42 (dd, 2H, *J* 4.7, 1.0, terminal th 5-H's), 7.51 (d, 2H, *J* 7.8, py 3/5-H's), 7.53 (d, 2H, *J* 7.1, py 5/3-H's), 7.67 (dd, 2H, *J* 4.2, 1.0, terminal th 3-H's), 7.67 (s, 2H, mid th), 7.65–7.72 (dd, 2H, *J* 7.1, 7.8, py 4-H's); MS (EI, *m*/*z*) 402; ν_{max}(KBr/cm^{-1}) 1581, 1560, 1447, 1426, 1266, 1158, 853, 796, 696, 518.

2,6-Bis{2-[2-(2-thienyl)-6-pyridyl]-5-thienyl}pyridine TPTPTPT 9

Method 1. To a stirred mixture of magnesium turnings (0.24 g, 9.87 mmol) in dry tetrahydrofuran (20 mL) under nitrogen was added dropwise 1,2-dibromoethane (1.85 g, 9.85 mmol) in dry THF (30 mL), the Grignard reaction was initiated by gently warming and the mixture was heated at reflux for 50 min, then the reaction mixture was cooled in an ice bath to 0 °C. In a separate flask, to a stirred mixture of TPT (1.0 g, 4.0 mmol) in dry tetrahydrofuran (20 mL) at −40 °C under nitrogen was slowly added n-butyllithium (5.5 mL, 1.64 mmol ml^{-1}, 9.02 mmol), the mixture was stirred for 30 min at −40 °C and then was slowly warmed to 0 °C for another 30 min. This solution was cooled to −60 °C and the above $MgBr_2$ solution was added slowly. After a further 30 min at −60 °C, the solution was slowly warmed to ambient temperature to afford the bis-Grignard reagent **7**. To this was added a solution of 2-bromo-6-

(2-thienyl)pyridine (2.41 g, 0.01 mol) and $PdCl_2$(dppb) (0.015 g, 0.0248 mmol) in dry tetrahydrofuran (20 mL) and the mixture was heated at reflux for 4 h. Most of the solvent was removed under reduced pressure and chloroform (100 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride (100 mL) and then water (100 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography (dichloromethane–light petroleum, 1:1) and then recrystallised from chloroform–light petroleum to give *TPTPTPT* **9** as pale yellow crystals (1.24 g, 57%), mp 117.5–118.5 °C (Found: C, 66.2; H, 3.3; N, 7.4. $C_{31}H_{19}N_3S_4$ requires C, 66.3; H, 3.4; N, 7.45%); $\delta_H(CDCl_3)$: 7.12 (dd, 2H, *J* 4.7, 4.8, th), 7.39 (dd, 2H, *J* 4.7, 1.0, th 2-H), 7.50 (d, 2H, *J* 7.8, py), 7.53 (d, 4H, *J* 8.1, py), 7.64–7.71 (m, 9H, py 3-H and th 6-H) (see formula **9** for full assignment); ν_{max}(KBr/cm^{-1}) 2360, 2340, 1580, 1560, 1538, 1447, 1435, 1265, 1159, 789, 701.

Method 2. To a stirred mixture of magnesium turnings (0.13 g, 5.34 mmol) in dry tetrahydrofuran (20 mL) under nitrogen was added dropwise 1,2-dibromoethane (0.995 g, 5.30 mmol) in dry tetrahydrofuran (30 mL), the reaction being initiated by gently warming and then the mixture heated at reflux for 50 min and cooled to 0 °C. In a separate flask, to a stirred mixture of TPT (1.2 g, 4.8 mmol) in dry tetrahydrofuran (20 mL) at −40 °C under nitrogen, was slowly added n-butyllithium (3.1 mL, 1.64 mmol ml^{-1}, 5.08 mmol); the mixture was stirred for 30 min at −40 °C and then was slowly warmed to 0 °C for another 30 min. This solution was cooled to −60 °C and the above magnesium bromide solution was added slowly. After a further 30 °C at −60 °C, the solution was slowly warmed to ambient temperature to give the Grignard reagent. To this Grignard reagent solution was added a solution of 2,6-dibromopyridine (0.56 g, 2.36 mmol) and $PdCl_2$(dppb) (0.010 g, 0.0165 mmol) in dry tetrahydrofuran (20 mL), and the mixture was heated at reflux for 4 h. Most of the solvent was removed under reduced pressure and chloroform (100 mL) was added. The reaction was worked up as above to give TPTPTPT **9** as pale yellow crystals (1.09 g, 82%).

2,5-Bis(2-bromo-6-pyridyl)thiophene (BrPTPBr) 10

Method 1. To a stirred mixture of magnesium turnings (0.82 g, 0.034 mol) in dry tetrahydrofuran (50 mL) under nitrogen was added dropwise 1,2-dibromoethane (5.8 g, 0.031 mmol) in dry tetrahydrofuran (30 mL). The reaction was initiated by gently warming and the mixture was heated at reflux for 50 min and then cooled to 0 °C. In a separate flask, to a stirred mixture of thiophene (1.0 g, 0.012 mol) in dry tetrahydrofuran (50 mL) at −40 °C under nitrogen was slowly added n-butyllithium (18.3 mL, 1.64 mmol ml^{-1}, 0.030 mol); the mixture was stirred for 30 min and then was slowly warmed to reflux for another 30 min. This solution was cooled to −60 °C and the above magnesium bromide solution was added slowly. After a further 30 min at −60 °C the solution was slowly warmed to ambient temperature to give the thiophene-2,5-bis-Grignard reagent. To this bis-Grignard reagent solution was added a solution of 2,6-dibromopyridine (5.63 g, 0.024 mol) and $PdCl_2$(dppb) (0.38 g, 0.629 mmol) in THF (20 mL) and the mixture was stirred at room temperature for 10 h. Most of the THF was removed under reduced pressure and dichloromethane (100 mL) was added. The organic layer was washed with saturated ammonium chloride solution (100 mL) and then water (100 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography (dichloromethane–light petroleum, 1:1) and then recrystallised from chloroform–light petroleum solution to give *2,5-bis(2-bromo-6-pyridyl)thiophene* (BrPTPBr) **10** as yellow crystals (1.50 g, 32%), mp 160.4–161.5 °C (Found: C, 42.3; H, 2.0; N, 7.2. $C_{14}H_8Br_2N_2S$ requires C, 42.4; H, 2.0; N, 7.1%); $\delta_H(CDCl_3)$: 7.35 (dd, 2H, *J* 7.6, 1.1, py 3-H's), 7.54 (dd, 2H, *J* 7.6, 8.1, py 4-H's), 7.62 (dd, 2H, *J* 8.1, 1.1, py 5-H's), 7.64 (s, 2H, th); MS (EI, *m*/*z*) 394, 396, 398; ν_{max}(KBr/cm^{-1}) 2359, 2341, 1576, 1556, 1546, 1530, 1428, 1162, 1127, 1117, 1009, 979, 780, 751, 739, 645.

Method 2. A mixture of magnesium turnings (0.41 g, 16.8 mmol), 2,5-dibromothiophene (2.0 g, 8.27 mmol) and three drops of 1,2-dibromoethane in dry tetrahydrofuran (40 mL) was heated at reflux for 18 h to form a white precipitate. The mixture was cooled to 0–5 °C and to this solution was slowly added a mixture of 2,6-dibromopyridine (3.92 g, 16.55 mmol) and $PdCl_2$(dppb) (0.10 g, 0.165 mmol) in dry tetrahydrofuran (30 mL). The reaction mixture was then heated at reflux for 4 h under nitrogen. After the above work-up 2,5-bis(2-bromo-6-pyridyl)thiophene (BrPTPBr) **10** was obtained as yellow crystals (0.65 g, 20%).

2,6-Bis[2-(2-methyl-6-pyridyl)-5-thienyl]pyridine (Me-PTPTP-Me) 11

The bis-Grignard reagent **7** of TPT (1.64 g, 6.74 mmol) in dry tetrahydrofuran (25 mL) was made as above. To this bis-Grignard reagent solution was added a solution of 2-bromo-6-methylpyridine (2.58 g, 0.015 mol) and $PdCl_2$(dppb) (0.24 g, 0.4 mmol) in dry tetrahydrofuran (15 mL) and the mixture was heated at reflux for 4 h. Tetrahydrofuran was removed and dichloromethane (100 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride (100 mL) and water (100 mL) and dried over magnesium sulfate. After evaporation, the crude product was flash chromatographed (light petroleum–dichloromethane, 1:1) and recrystallised from dichloromethane–methanol to give *Me-PTPTP-Me* **11** as yellow crystals (1.30 g, 52%), mp 184–186 °C (Found: C, 70.3; H, 4.6; N, 9.7. $C_{25}H_{19}N_3S_2$ requires C, 70.6; H, 4.5; N, 9.9%); $\delta_H(CDCl_3)$: 2.62 (s, 6H, Me's), 7.03 (dd, 2H, *J* 7.6, 1.1, terminal py 3-H's), 7.50 (dd, 2H, *J* 7.6, 7.8, terminal py 4-H's), 7.51 (dd, 2H, *J* 7.8, 1.1, terminal py 5-H's), 7.55 (d, 2H, *J* 7.4, mid-py β-H's), 7.60 (d, 2H, *J* 4.1, th), 7.65 (t, 1H, *J* 7.4, mid-py 4-H), 7.68 (d, 2H, *J* 4.1, th); ν_{max}(KBr/cm^{-1}) 2924, 1583, 1561, 1450, 1434, 1267, 1232, 1163, 1096, 782, 674.

Attempted synthesis of Me-PTPTPTP-Me

To a stirred mixture of magnesium turnings (0.094 g, 7.87 mmol) in dry tetrahydrofuran (30 mL) under nitrogen was added dropwise 1,2-dibromoethane (1.34 g, 7.15 mmol) in dry tetrahydrofuran (10 mL), the reaction being initiated by gently warming, and the mixture was heated at reflux for 50 min. In a separate flask, to a stirred mixture of TPTPT **8** (1.200 g, 2.98 mmol) in dry tetrahydrofuran (35 mL) at −40 °C under nitrogen was slowly added n-butyllithium (4.36 mL, 1.64 mmol ml^{-1}, 7.15 mmol); the mixture was stirred for 30 min and then slowly warmed to room temperature for 1 h. This solution was cooled to −60 °C and the above $MgBr_2$ solution was added slowly. After a further 30 min at −60 °C the solution was slowly warmed to ambient temperature. To this solution was added a solution of 2-bromo-6-methylpyridine (1.012 g, 5.89 mmol) and $PdCl_2$(dppb) (0.10 g, 0.16 mmol) in dry tetrahydrofuran (13 mL) and the mixture was heated at reflux for 4 h. Tetrahydrofuran was removed and dichloromethane (100 mL) was added. The solution was washed with saturated aqueous ammonium chloride (100 mL) and then water (100 mL) and dried over magnesium sulfate. After flash chromatography (light petroleum–dichloromethane, 1:1) the main compound was found to be starting material with no evidence of Me-PTPTPTP-Me.

Attempted synthesis of $BrCH_2$-PTPTP-CH_2Br 12

A mixture of Me-PTPTP-Me **11** (0.5 g, 1.17 mmol), *N*-bromosuccinimide (0.50 g, 2.81 mmol) and benzoyl peroxide (0.05 g)

in benzene (24 mL) was heated at reflux for 4 h, with vigorous stirring under nitrogen. The flask was cooled, and the insoluble succinimide was filtered and washed once with dry benzene. The organic layer was evaporated under reduced pressure, and aqueous sodium hydroxide (50 mL, 2 M) was added to the residue. The aqueous layer was extracted with dichloromethane (50 mL). The organic phase was washed with water (50 mL) and saturated sodium chloride solution (50 mL) and dried over magnesium sulfate. The crude product was subjected to column chromatography but no pure product was obtained.

2-Bromo-6-*tert*-butylsulfanylmethylpyridine

Direct synthesis. A mixture of 2-bromo-6-methylpyridine (1.4 g, 8.14 mmol), *N*-bromosuccinimide (1.45 g, 8.14 mmol) and benzoyl peroxide (0.01 g) in dry carbon tetrachloride (20 mL) was heated at reflux for 4 h with vigorous stirring under nitrogen. Precipitated succinimide was filtered off at room temperature, the organic layer was washed with sodium hydroxide solution (2 × 20 mL, 4%) and water (2 × 20 mL), and dried over magnesium sulfate. After evaporation under reduced pressure, the resulting white solid was dissolved in absolute ethanol (30 mL), and then *tert*-butyl thiol (0.8 g, 8.87 mmol) was added, followed by sodium hydroxide (0.40 g, ~10 mmol). The reaction mixture was stirred at room temperature for 1 h under nitrogen. The organic layer was evaporated under reduced pressure, dichloromethane (30 mL) was added to the residue, then the organic phase was washed with saturated sodium chloride solution (30 mL) and water (30 mL) and dried over magnesium sulfate. After evaporation, the crude product was flash chromatographed (light petroleum–dichloromethane, 3:7) to give *2-bromo-6-tert-butylsulfanylmethylpyridine* as a colourless liquid (1.06 g, 50%), which solidified overnight at room temperature. $\delta_H(CDCl_3)$: 1.33 (s, 9H, t-Bu), 3.89 (s, 2H, CH_2), 7.33 (dd, 1H, *J* 7.8, 1.1, py 5-H), 7.44 (dd, 1H, *J* 7.6, 1.1, py 3-H), 7.50 (dd, 1H, *J* 7.8, 7.6, py 4-H); MS (EI+, *m*/*e*) 259, 261 [Found: 259.0083. $C_{10}H_{14}BrNS$ requires 259.0030]. ν_{max}(KBr/cm^{-1}) 2959, 2920, 2897, 2859, 1580, 1549, 1439, 1404, 1361, 1172, 1154, 1139, 1109, 1075, 985, 875, 801, 747, 708, 669, 606, 519; a small amount of 2-bromo-6-dibromomethylpyridine[27] was also isolated, mp 82.5–83.5 °C (lit.,[27] mp 83–84 °C) (8%).

Method 2. To a mixture of 2-bromo-6-bromomethylpyridine (2.00 g, 7.97 mmol) in absolute ethanol (50 mL) was added *tert*-butyl thiol (1.5 g, 16.6 mmol), followed by sodium hydroxide (0.6 g, 15 mmol). The reaction mixture was stirred at room temperature for 1 h under nitrogen. The organic layer was evaporated under reduced pressure, dichloromethane (50 mL) added to the residue, and the organic phase washed with saturated sodium chloride solution (50 mL) and water (50 mL) and dried over magnesium sulfate. After evaporation, the crude product was flash chromatographed (light petroleum–dichloromethane, 3:7) to give 2-bromo-6-*tert*-butylsulfanylmethylpyridine as a colourless liquid (1.77 g, 86%), which solidified overnight.

2,6-Bis[2-(2-*tert*-butylsulfanylmethyl-6-pyridyl)-5-thienyl]-pyridine ($^tBuSCH_2$-PTPTP-CH_2SBu^t) 13

To a stirred mixture of magnesium turnings (0.157 g, 6.71 mmol) in dry tetrahydrofuran (30 mL) under nitrogen was added dropwise 1,2-dibromoethane (1.16 g, 6.12 mmol) in dry tetrahydrofuran (20 mL) and the mixture was heated at reflux for 50 min. In a separate flask, to a stirred mixture of TPT **2** (0.446 g, 1.85 mmol) in dry tetrahydrofuran (30 mL) at −40 °C under nitrogen was slowly added n-butyllithium (3.0 mL, 1.64 mmol ml^{-1}, 4.92 mmol) and the mixture stirred for 30 min and slowly warmed to room temperature. After 1 h the solution was cooled to −60 °C and the above magnesium bromide solution was added slowly. After a further 30 min at −60 °C, the solution was slowly warmed to ambient temperature to give the bis-Grignard reagent. To this bis-Grignard reagent solution was added a solution of 2-bromo-6-*tert*-butylsulfanylmethylpyridine (0.99 g, 3.82 mmol) and $PdCl_2$(dppb) (0.09 g, 0.15 mmol) in dry tetrahydrofuran (15 mL) and the mixture was heated at reflux for 4 h. The solvent was removed and dichloromethane (50 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride (50 mL) and water (50 mL) and dried over magnesium sulfate. After evaporation, the crude product was flash chromatographed (light petroleum–dichloromethane, 1:1) and recrystallised from dichloromethane–methanol to give *the title* product as yellow crystals (0.60 g, 54%), mp 180–182 °C (Found: C, 65.7; H, 5.7; N, 7.1. $C_{33}H_{35}N_3S_4$ requires C, 65.9; H, 5.9; N, 7.0%); $\delta_H(CDCl_3)$: 1.39 (s, 18H, t-Bu), 3.99 (s, 4H, CH_2), 7.33 (d, 2H, *J* 7.8, py), 7.51–7.72 (m, 11H, py and th H's); ν_{max}(KBr/cm^{-1}) 2960, 2939, 2923, 2897, 2859, 1585, 1562, 1448, 1437, 1364, 1313, 1264, 1214, 1165, 988, 797, 749, 671.

Attempted de-*tert*-butylation of $^tBuSCH_2$-PTPTP-CH_2SBu^t 13

A mixture of $^tBuSCH_2$-PTPTP-CH_2SBu^t **13** (0.89 g, 1.46 mmol), mercury acetate (0.93 g, 2.91 mmol) and anisole (0.5 mL) in trifluoroacetic acid (20 mL) was stirred at 0 °C for 30 min, and hydrogen sulfide gas was passed through the solution for a further 30 min. Most of the trifluoroacetic acid was distilled off under reduced pressure and dichloromethane (50 mL) was added to the solution. The precipitate was then filtered by suction and the organic layer was washed with aqueous sodium hydroxide (50 mL, 5 M) and water (50 mL) and dried over magnesium sulfate. After evaporation, an insoluble complex mixture was obtained as a yellow solid. The infrared spectrum of the crude product showed no S–H bonds (usually a small peak between ν_{max} 2540–2600 cm^{-1}).

Attempted reaction between bromomethylbenzene and *tert*-butylsulfanylmethylbenzene

A mixture of bromomethylbenzene (0.35 g, 1.94 mmol), *tert*-butylsulfanylmethylbenzene (0.35 g, 2.04 mmol) and *N*-diisopropylethylamine (0.5 g) in acetonitrile (12 mL) was heated at reflux for 12 h. TLC only showed starting materials. The same reaction but using xylene instead of acetonitrile also gave no reaction.

Attempted synthesis of 2,6-bis[2-(2-sulfanylmethyl-6-pyridyl)-5-thienyl]pyridine $HSCH_2$-PTPTP-CH_2SH from Me-PTPTP-Me 11

To a stirred mixture of CH_3-PTPTP-CH_3 **11** (0.153 g, 0.359 mmol) in dry tetrahydrofuran (20 mL) at 0 °C under nitrogen was slowly added n-butyllithium (0.6 mL, 1.64 mmol mL^{-1}, 0.984 mmol), the mixture stirred for 30 min and then slowly warmed to room temperature for another 30 min. This solution was then cooled to 0 °C and sulfur (0.035 g, 1.09 mmol) was added. After a further 30 min in an ice bath, the mixture was slowly warmed to room temperature for another half hour. After separation, only starting material was obtained.

2-Bromo-6-hydroxymethylpyridine[24]

Method 1. To a stirred mixture of 2,6-dibromopyridine (3.0 g, 12.7 mmol) in dry THF (40 mL) at −70 °C under nitrogen was slowly added n-butyllithium (5.08 mL, 2.50 mmol mL^{-1}, 12.7 mmol) and the mixture stirred for 30 min and then slowly warmed to −40 °C for another 30 min. This solution was cooled to −70 °C and dimethylformamide (2.01 mL, 26.3 mmol) in THF (15 mL) was added slowly over 10 min. After a further 30 min at −70 °C, the solution was slowly warmed to −20 °C and quenched with methanol (20 mL). Sodium borohydride (487 mg, 12.9 mmol) was added to the mixture in portions at −10 °C and the mixture was slowly warmed to room temperature. After addition of acetone (1.5 mL), the mixture

was diluted with ethyl acetate (100 mL). The organic phase was washed with water (50 mL) and saturated sodium chloride solution (50 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography (ethyl acetate–light petroleum, 1 : 5) to give 2-bromo-6-hydroxymethylpyridine as a white solid (1.45 g, 61%), mp 32–33 °C (lit.,[24] mp 32–33 °C); $\delta_H(CDCl_3)$: 4.85 (s, 2H, CH_2), 7.37 (d, 1H, *J* 7.7, py 5-H), 7.46 (d, 1H, *J* 7.7, py 3-H), 7.56 (t, 1H, *J* 7.7, py 4-H).

Method 2. To a stirred mixture of 2-bromopyridine-6-carbaldehyde (1.0 g, 5.37 mmol) in methanol (20 mL) at −10 °C was added sodium borohydride (250 mg, 6.60 mmol). The mixture was slowly warmed to room temperature. After addition of acetone (1.0 mL), the mixture was diluted with ethyl acetate (30 mL). The organic phase was washed with water (30 mL) and saturated sodium chloride solution (30 mL), and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography (ethyl acetate–light petroleum, 1 : 5) to give 2-bromo-6-hydroxymethylpyridine as a white solid (0.91 g, 90%).

Method 3. To a stirred mixture of 2,6-dibromopyridine (3.0 g, 12.6 mmol) in dry tetrahydrofuran (40 mL) at −70 °C under nitrogen was slowly added n-butyllithium (7.7 mL, 1.64 mmol mL^{-1}, 12.6 mmol), the reaction mixture was stirred for 30 min, and then paraformaldehyde (0.45 g, 14.8 mmol) in tetrahydrofuran (20 mL) was slowly added at −70 °C. The reaction mixture was stirred for another 30 min and then slowly warmed to −40 °C. Distilled water (0.5 mL) was then slowly added to the solution. Most of the tetrahydrofuran was removed under reduced pressure, ether (100 mL) added, the ether layer washed with distilled water (100 mL) and saturated sodium chloride solution (100 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography (dichloromethane) to give 2-bromopyridine as the main product (1.8 g, 90%).

2,6-Bis[2-(2-hydroxymethyl-6-pyridyl)-5-thienyl]pyridine $HOCH_2$-PTPTP-CH_2OH 15

To a stirred mixture of magnesium turnings (0.575 g, 23.6 mmol) in dry tetrahydrofuran (70 mL) under nitrogen was added dropwise 1,2-dibromoethane (4.44 g, 23.6 mmol) in dry tetrahydrofuran (10 mL). The reaction was initiated by gentle warming and then the mixture was heated at reflux for 50 min and cooled in ice. In a separate flask, to a stirred mixture of TPT (2.0 g, 8.22 mmol) in dry tetrahydrofuran (50 mL) at −40 °C under nitrogen was slowly added n-butyllithium (7.89 mL, 2.50 mmol mL^{-1}, 19.7 mmol). The mixture was stirred for 30 min at −40 °C and then slowly warmed to room temperature for another 30 min. This solution was cooled to −60 °C and the above magnesium bromide solution was added slowly. After a further 30 min at −60 °C, the solution was slowly warmed to ambient temperature to give the Grignard reagent. To this solution was added a solution of 2-bromo-6-(tetrahydro-2*H*-pyran-2-yloxymethyl)pyridine (4.47 g, 16.4 mmol) and $PdCl_2$ (dppb) (0.20 g) in tetrahydrofuran (18 mL) and the mixture heated at reflux under nitrogen for 4 h. Most of the solvent was removed under reduced pressure and dichloromethane (100 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride (100 mL), water (100 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography (elution: 80% dichloromethane–20% ethyl acetate) and then recrystallised from chloroform–light petroleum to give *bis-α-(tetrahydropyran-2-yloxymethyl)-PTPTP* **14** as yellow crystals (3.49 g, 68%), mp 155.5–157 °C (Found: C, 67.0; H, 5.6; N, 6.9. $C_{35}H_{35}N_3O_4S_2$ requires C, 67.2; H, 5.6; N, 6.7%); $\delta_H(CDCl_3)$: 1.60–1.92 (m, 12H, CH_2), 3.57–4.02 (m, 4H, CH_2), 4.71–5.00 (m, 6H, CH_2-H and CH-H), 7.35–7.39 (d, 2H, *J* 7.6, py), 7.50–7.54 (d, 2H, *J* 7.3, py), 7.58–7.75 (m, 9H, th H and py H); ν_{max}(KBr/cm^{-1}) 2937, 2863, 2849, 1587, 1571, 1562, 1450, 1382, 1343, 1320, 1293, 1199, 1155, 1128, 1074, 1035, 971, 906, 868, 784.

To a stirred mixture of bis-α-(tetrahydropyran-2-yloxymethyl)-PTPTP **14** (1.09 g, 1.74 mmol) in dichloromethane (30 mL) and methanol (8 mL) was added hydrochloric acid (35%, 8 drops). The reaction mixture was stirred at room temperature for 3 h. The resulting precipitate was filtered and washed with sodium hydroxide solution (1 M) then distilled water, methanol, dichloromethane and ether and air dried to give the *$HOCH_2$-PTPTP-CH_2HO* **15** as a yellow solid (0.73 g, 92%), mp 200–202 °C; $\delta_H(CF_3CO_2D)$: 5.45 (s, 4H, CH_2), 8.07–8.72 (m, 13H, th H and py H); ν_{max}(KBr/cm^{-1}) 3264 (br OH), 3084, 3065, 1629, 1613, 1561, 1433, 1391, 1269, 1175, 1100, 791.

Attempted synthesis of bis-α-methylsulfonylmethyl-PTPTP 16

To a suspension of $HOCH_2$-PTPTP-CH_2OH **15** (0.70 g, 1.53 mmol) and triethylamine (2 mL) in dichloromethane at 0 °C was added methanesulfonyl chloride (0.4 g, 3.49 mmol). The reaction mixture was stirred for 30 min at 0 °C and then was slowly warmed to room temperature for another 1 h. The starting material remained insoluble and did not react. Further methanesulfonyl chloride (1 mL) was added to the solution at room temperature when the reaction mixture became clear immediately. The solution was treated with saturated brine and the organic phase washed with water and dried with magnesium sulfate. After removal of the solvent, a thick oil remained which showed numerous spots on TLC. Attempted flash chromatography gave no pure material. Proton NMR ($CDCl_3$) of the crude product revealed a complex mixture of products.

2,6-Bis(methylsulfonylmethyl)pyridine

To a mixture of 2,6-bis(hydroxymethyl)pyridine (5.0 g, 36 mmol) and triethylamine (9.1 g, 90 mmol) in dichloromethane (70 mL) at 0 °C was added dropwise with stirring under a nitrogen atmosphere, methanesulfonyl chloride (8.25 g, 72 mmol). The reaction mixture was stirred for 30 min at 0 °C and then was slowly warmed to room temperature for another 1 h. The solution was treated with saturated brine and the organic phase washed with water and dried with magnesium sulfate. The crude product was purified by flash chromatography (dichloromethane) to give *2,6-bis(methylsulfonylmethyl)pyridine* (9.03 g, 85% yield) as a colourless solid, mp 73–74.5 °C (Found: 295.0165. $C_9H_{13}NO_6S_2$ requires 295.0184); $\delta_H(CDCl_3)$: 3.12 (s, 6H, Me's), 5.31 (s, 4H, CH_2), 7.47 (d, 2H, *J* 7.6, py H's); ν_{max}(KBr/cm^{-1}) 3032, 3008, 2930, 1599, 1464, 1352, 1333, 1176, 1027, 1009, 982, 957, 845, 820, 783.

Bis(2-hydroxymethyl-6-pyridylmethyl)sulfide 19

$Na_2S{\cdot}9H_2O$ (1.19 g, 4.95 mmol) in ethanol (80 mL) and toluene (55 mL) was dried by azeotropic distillation at 73 °C. To this mixture was added 2-bromomethyl-6-hydroxymethylpyridine (2.0 g, 9.90 mmol) and the reaction mixture heated at reflux for 2 h. The solvent was removed under reduced pressure and dichloromethane (70 mL) was added to the residue. The organic phase was washed with saturated sodium chloride solution (70 mL) and water (70 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography (dichloromethane–methanol, 95 : 5) to give the dimer as a viscous liquid which solidified overnight as a waxy solid (1.40 g, 51%), mp 74–75.5 °C; MS (ES, MH^+) 277 (Found 277.0930. $C_{14}H_{16}N_2O_2S$ requires 276.0932); $\delta_H(CDCl_3)$: 3.71 (s, 4H, CH_2), 4.64 (br s, 2H, OH), 4.64 (s, 4H, CH_2OH), 7.04 (d, 2H, *J* 7.8, pyridine), 7.20 (d, 2H, *J* 7.8, pyridine), 7.54 (t, 2H, *J* 7.8, pyridine); ν_{max}(KBr/cm^{-1}) 3175, 2933, 1594, 1574, 1458, 1409, 1372, 1160, 1149, 1031, 1005, 990, 901, 837, 803, 754, 711, 695, 654, 643.

Attempted synthesis of bis(2-methylsulfonylmethyl-6-pyridylmethyl) sulfide

To a stirred mixture of the sulfide **19** (1.0 g, 3.62 mmol) and triethylamine (1.26 mL, 9.04 mmol) in chloroform (50 mL) in an ice bath under nitrogen was added dropwise methanesulfonyl chloride (0.83 g, 7.24 mmol) in chloroform (10 mL). The reaction mixture was stirred in an ice bath for 4 h. Only starting material was found on TLC. Thus, the reaction temperature was raised to room temperature for another 12 h, and more methanesulfonyl chloride (0.83 g, 7.24 mmol) was slowly added. A mixture of products was obtained according to TLC, which could not be separated by chromatography.

2,6-Bis(2-hydroxymethyl-6-pyridylmethylsulfonylmethyl)-pyridine 20

A mixture of 2-bromomethyl-6-hydroxymethylpyridine (1.53 g, 7.6 mmol), 2,6-bis(sulfanylmethyl)pyridine (0.65 g, 3.8 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.16 g, 7.6 mmol) in dry THF (60 mL) was heated at reflux for 48 h under nitrogen. THF was removed under reduced pressure and dichloromethane (50 mL) was added to the residue. The organic phase was washed with saturated sodium chloride solution (50 mL) and water (50 mL) and dried over magnesium sulfate. After evaporation, the crude product was purified by flash chromatography (dichloromethane–methanol, 95 : 5) to give the *title product* **20** as a viscous liquid which solidified overnight as a waxy solid (1.34 g, 85%), mp 70–72 °C; *m*/*z* (ES, MH^+) 414 [Found 414.1230. $C_{21}H_{23}N_3O_2S_2$ requires 413.1232]; $\delta_H(CDCl_3)$: 3.81 (s, 4H, CH_2), 3.83 (s, 4H, CH_2), 4.71 (br s, 2H, OH), 4.71 (s, 4H, CH_2OH), 7.08 (d, 2H, *J* 7.6, py), 7.25 (d, 2H, *J* 7.6, py), 7.27 (d, 2H, *J* 7.6, py), 7.60 (t, 1H, py), 7.60 (t, 2H, *J* 7.6, py); ν_{max}(KBr/cm^{-1}) 3493, 3227, 1592, 1572, 1454, 1422, 1349, 1214, 1153, 1087, 1067, 1052, 1001, 817, 754.

Attempted synthesis of 2,6-bis(2-methylsulfonylmethyl-6-pyridylmethylsulfanylmethyl)pyridine

To a stirred mixture of the above compound **20** (1.57 g, 3.80 mmol) and triethylamine (0.96, 9.49 mmol) in chloroform (50 mL) under nitrogen in an ice bath, was added dropwise methanesulfonyl chloride (0.87 g, 7.6 mmol) in chloroform (10 mL). The reaction mixture was stirred in an ice bath for 4 h when only starting material was observed by TLC. Thus, the reaction temperature was raised to room temperature for another 12 h, and then more methanesulfonyl chloride (0.87 g, 7.6 mmol) and triethylamine (0.96 g, 9.49 mmol) were slowly added. An inseparable mixture was obtained according to TLC. Attempted separation by chromatography was unsuccessful.

Synthesis of complexes of ligands 19 and 20 with transition metal ions: general method

Equimolar solutions of the appropriate MCl_2 ($M = Co^{2+}$, Ni^{2+} or Zn^{2+}) salt and ligand **19** or **20** in ethanol were allowed to stand at room temperature for several hours. A coloured precipitate appeared which was filtered, washed with ethanol, and vacuum dried.

19·$CoCl_2$. Pink crystals from methanol–ethyl acetate, mp 228–230 °C (decomp.) (Found: C, 41.5; H, 4.0; N, 6.8. $C_{14}H_{16}Cl_2CoN_2O_2S$ requires C, 41.4; H, 4.0; N, 6.9%); MS (FAB) 370; $C_{14}H_{16}Cl_2CoN_2O_2S$ − Cl requires 370; ν_{max}(KBr/cm^{-1}) 3429, 2597, 2359, 1601, 1577, 1460, 1403, 797, 783, 604.

20·$CoCl_2$. Blue crystals from methanol–ethyl acetate, mp 140–148 °C (decomp.) (Found: C, 46.4; H, 4.3; N, 7.7. $C_{21}H_{23}Cl_2CoN_3O_2S_2$ requires C, 46.4; H, 4.3; N, 7.7%); MS (FAB) 471; $C_{21}H_{23}Cl_2CoN_3O_2S_2$ − HCl_2 requires 471; ν_{max}(KBr/cm^{-1}) 3422, 3067, 2594, 1601, 1574, 1455, 1402, 1021, 797.

19·$NiCl_2$. Green crystals from methanol–ethyl acetate, mp 250–254 °C (decomp.) (Found: C, 41.4; H, 4.0; N, 6.7. $C_{14}H_{16}Cl_2N_2NiO_2S$ requires C, 41.4; H, 4.0; N, 6.9%); MS (FAB) 369; $C_{14}H_{16}Cl_2N_2NiO_2S$ − Cl requires 369; ν_{max}(KBr/cm^{-1}) 3449, 3380, 3200, 1604, 1574, 1453, 1430, 1045, 819, 805, 755, 631.

20·$NiCl_2$. Blue crystals from methanol–propan-2-ol, mp 187–190 °C (decomp.) (Found: C, 46.4; H, 4.3; N, 7.7. $C_{21}H_{23}Cl_2N_3NiO_2S_2$ requires C, 46.4; H, 4.3; N, 7.7%); MS (FAB) 470; $C_{21}H_{23}Cl_2N_3NiO_2S_2$ − HCl_2 requires 470; ν_{max}(KBr/cm^{-1}) 3400, 2932, 2726, 2616, 1603, 1575, 1454, 1042, 808, 758, 625.

19·$ZnCl_2$. White crystals from methanol, mp 210–212 °C (decomp.) (Found: C, 40.8; H, 3.8; N, 6.7. $C_{14}H_{16}Cl_2N_2O_2SZn$ requires C, 40.75; H, 3.9; N, 6.8%); $\delta_H(CD_3OD)$: 4.04 (s, 4H, CH_2S), 4.87 (s, 4H, CH_2O), 7.44 (d, 2H, *J* 8.1, py H), 7.47 (d, 2H, *J* 8.1, py H), 7.93 (t, 2H, py H); MS (FAB) 375; $C_{14}H_{16}Cl_2N_2O_2SZn$ − Cl requires 375; ν_{max}(KBr/cm^{-1}) 3441, 2360, 1599, 1573, 1433, 1406, 1071, 1051, 793, 766.

20·$ZnCl_2$. White crystals from methanol, mp 189–191 °C (decomp.) (Found: C, 45.9; H, 4.3; N, 7.6. $C_{21}H_{23}Cl_2N_3O_2S_2Zn$ requires C, 45.9; H, 4.2; N, 7.6%); $\delta_H(CD_3OD)$: 3.90 (s, 4H, CH_2S), 3.96 (s, 4H, CH_2O), 4.73 (s, 4H, CH_2O), 7.32 (d, 2H, *J* 8.1, py H), 7.36 (d, 2H, *J* 8.1, py H), 7.38 (d, 2H, *J* 8.1, py H), 7.69 (t, 1H, *J* 8.1, py H), 7.79 (t, 2H, *J* 8.1, py H); MS (FAB) 476; $C_{21}H_{23}Cl_2N_3O_2S_2Zn$ − HCl_2 requires 476; ν_{max}(KBr/cm^{-1}) 3432, 2360, 2341, 1601, 1590, 1573, 1454, 1442, 1067, 1021, 814, 756.

References

1 Part of this work appeared as a preliminary communication in: O. Meth-Cohn, Y. Zegui and J. Hui, *Electronic Conference on Current Trends in Organic Chemistry*, (ECTOC-1), eds. H. S. Rzepa and J. G. Goodman, Royal Society of Chemistry (CD-ROM), 1995.
2 O. Meth-Cohn and Z. Yan, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 423.
3 S. P. Stanforth, *Tetrahedron*, 1998, **54**, 6179.
4 T. Kauffmann, E. Wienhöfer and A. Woltermann, *Angew. Chem.*, *Int. Ed. Engl.*, 1971, **10**, 741.
5 K. Tamao, I. Kodama, M. Kumada, A. Minato and K. Syzuki, *Tetrahedron*, 1982, **38**, 3347.
6 S. Gronowitz and D. Peters, *Heterocycles*, 1990, **30**, 645.
7 S. W. Wright, D. L. Hageman and L. D. McClure, *J. Org. Chem.*, 1994, **5**, 6095.
8 A. Minato, K. Suzuki, K. Tamao and M. Kumada, *J. Chem. Soc.*, *Chem. Commun.*, 1984, 511.
9 R. M. Kellogg, A. P. Schaap, E. T. Harper and H. Wynberg, *J. Org. Chem.*, 1968, **33**, 2902.
10 O. Hinsberg, *Chem. Ber.*, 1910, **43**, 901.
11 F. Vögtle and L. Schunder, *Chem. Ber.*, 1969, **102**, 2677.
12 H. J. J.-B. Martel, S. McMahon and M. Rasmussen, *Aust. J. Chem.*, 1979, **32**, 1241.
13 R. H. Mitchell, R. H. T. Otsubo and V. Boekelheide, *Tetrahedron Lett.*, 1975, 219.
14 C. A. Salata, D. V. Engen and C. J. Burrows, *J. Chem. Soc.*, *Chem. Commun.*, 1988, 579.
15 D. D. Perrin and W. L. F. Armarego, *Purification of Organic Compounds*, 3rd edn., Pergamon, Oxford, 1988.
16 H. Meyer, *Monatsh. Chem.*, 1903, **24**, 206.
17 F. Barnes and P. Fales, *J. Am. Chem. Soc.*, 1953, **75**, 3830.
18 M. Newcomb, J. M. Timko, D. M. Walba and D. J. Cram, *J. Am. Chem. Soc.*, 1977, **99**, 6392.
19 US Pat. (Bristol Meyers) 3290319, 1966 (*Chem. Abstr.*, 1967, **66**, 115609).
20 G. R. Newkome, D. C. Pantaleo, W. E. Puckett, P. L. Ziefle and W. A. Deutsch, *J. Inorg. Nucl. Chem.*, 1981, **43**, 1529.
21 G. Ernst, *Synthesis*, 1992, 519.
22 L. Breau, N. K. Sharma, J. R. Butler and T. Durst, *Can. J. Chem.*, 1991, **69**, 185.
23 J. E. Parks, B. E. Wagner and R. H. Holm, *Inorg. Chem.*, 1971, **10**, 2472.
24 T. Hiroshi, U. Jun'ichi, H. Hiromi, K. Ken'ichi, T. Takakazu, W. Shoji and O. Shigero, *J. Org. Chem.*, 1993, **58**, 4389.
25 Y. Sugi and K. Bando, *Chem. Lett.*, 1976, 727.
26 S. W. Breuer and F. G. Thorpe, *Tetrahedron Lett.*, 1974, **42**, 3719.
27 E. Graf, *Synthesis*, 1992, 519.

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