

STANNYLATION REACTIONS AND CROSS-COUPPLINGS IN PYRIMIDINES

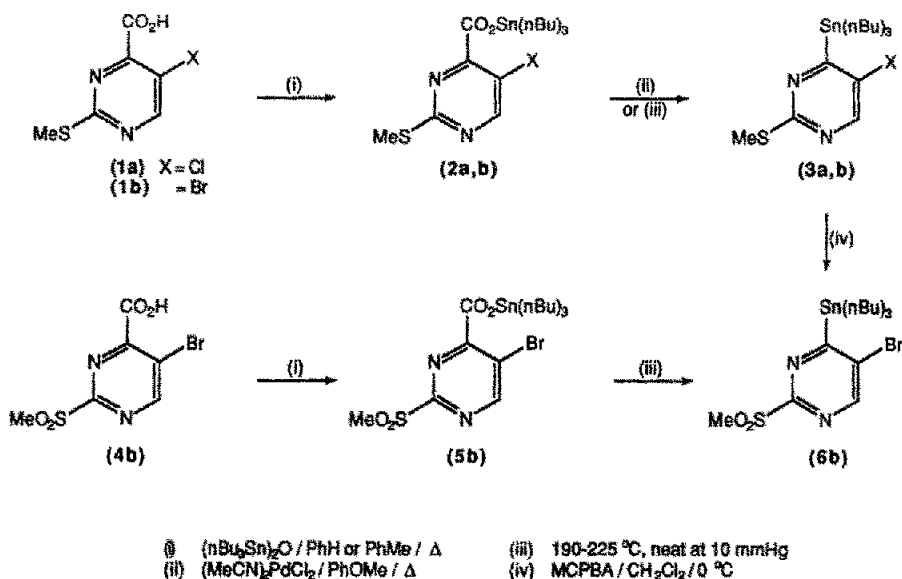
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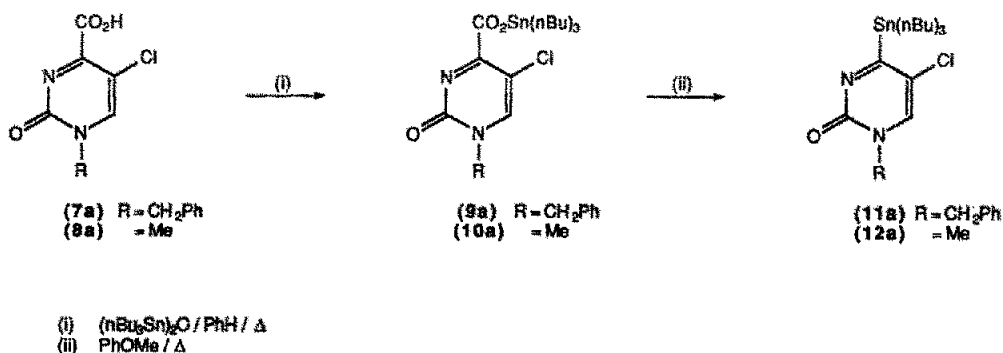
Summary: *Pyrimidines have been stannylated in the activated 4-position by thermal decarboxylation of the corresponding carboxylic organotin esters. The decarboxylation can be catalyzed by bis(acetonitrile)palladium(II) dichloride. 4-Iodopyrimidines are 4-stannylated either by substitution reactions with tri-n-butyltin-copper or by coupling reaction with hexamethyl- or hexa-n-butyl-ditin and Pd(II) catalysis. The stannylated pyrimidines form new carbon-carbon bonds by Pd(II)-catalyzed cross-couplings. tert-Butyldimethylsilyl-, dimethylhexylsilyl- and tert-butyldiphenylsilyl-oxymethyl(tri-n-butyl)tin have been synthesized and used in Pd(II)-catalyzed cross-coupling reactions with 4-chloropyrimidines. The silyl groups were not cleaved off during exposure to fluoride ions in aqueous media but were readily removed by fluoride ions in THF to yield the 4-hydroxymethylpyrimidine.*

Carbon-carbon bond formation in π -electron deficient heterocycles can be achieved in a two-step reaction which involves 1:1 adduct formation between the heterocycle and the organometallic reagent and a subsequent dehydrogenation of the adduct to the heteroaromatic system.¹ A more general method for carbon-carbon bond formation, however, is available by cross-coupling reactions. Thus carbon substituents can be introduced into aryl systems by way of the appropriate aryl bromides or iodides which will react with organotin reagents under the influence of palladium catalysis. Alternatively, the polarity in the reagents is reversed by reacting an aryltin derivative with an organo halide under the influence of the same catalyst.² The method of choice will depend on the relative availability, reactivity and stability of the reactants. We have explored both routes in developing methodology for substitutions in the biologically important pyrimidine system.³⁻⁵

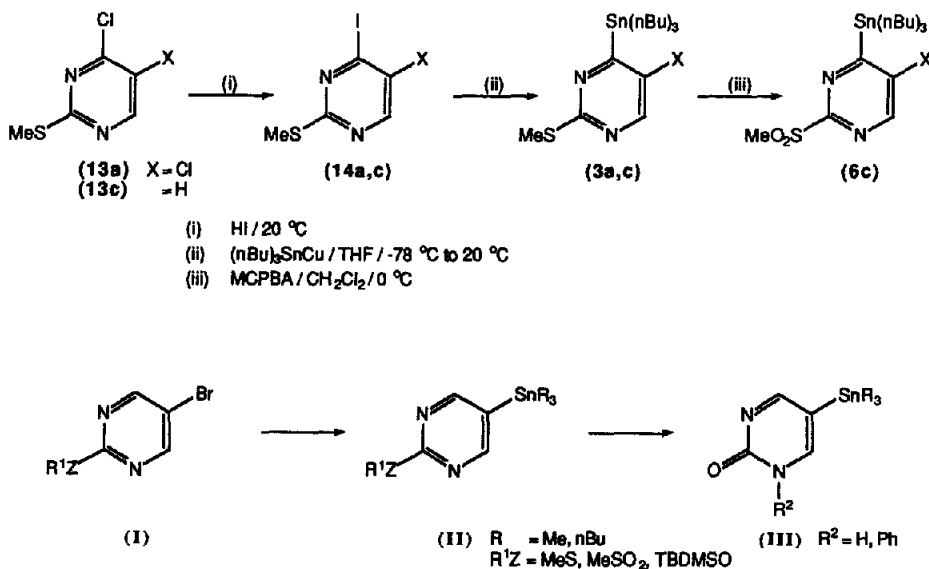
Stannylation is often effected by a transmetallation reaction between a stannyl halide and the appropriate lithiated species. Lithiated derivatives suitable for trans-stannylation in the 2,4,6-activated positions in the π -electron deficient pyrimidine system, however, are not readily available because of competitive adduct formation between the heterocycle and the lithium reagent, or between the heterocycle and its lithiated species acting as nucleophile.⁶ We have found that stannylation can be effected by decarboxylation of stannyl carboxylate esters. The decarboxylation is from an activated position. It has been known for some time that organotin esters of alkynyl and alkenyl carboxylic acids containing electron withdrawing substituents are decarboxylated on heating with formation of a carbon-metal bond as in the case of tri-n-butylstannyl phenylpropionate; stannylated fluorobenzenes have also been prepared by decarboxylation of the corresponding benzoic organotin esters.⁷

**Scheme 1**

The organotin carboxylates were prepared by reactions of the carboxylic acids (1a,b) and (4b) with bis(tri-*n*-butyltin) oxide with azeotropic removal of water. The carboxylates are characterized by CO absorption in IR at $1645\text{--}70\text{ cm}^{-1}$ in agreement with literature.⁸ Thermal decarboxylation reactions of the 2-methylthio derivatives (2a) and (2b) in anisole gave the 4-stannylated products in 30–40 % yield. Free radical conditions, AIBN and illumination, did not significantly affect the yield. Metal catalysis, however, did influence the reaction; Pd(II) complexes were best. With bis(acetonitrile)- and bis(triphenylphosphine)palladium(II) dichloride the yield of the 4-stannylated product was *ca.* 70 % after reflux for 4–6 hours in anisole. Tris(triphenylphosphine)rhodium(I) chloride, however, which is a decarbonylation catalyst, had only a slight effect on the decarboxylation reaction; yield 50 %. Decarboxylation of the 2-methylsulfonyl analogue (5b) of the sulfide (2b), however, was difficult to effect. The metal catalysts described above had little influence on the course of the reaction. The 4-stannyl-2-sulfonylpyrimidine (6b) was isolated in low yield after pyrolysis at 225°C for 10 min. Compound (6b), however, is available in satisfactory yield by chemoselective oxidation of the sulfide (3b) using MCPBA in dichloromethane at 0°C .

**Scheme 2**

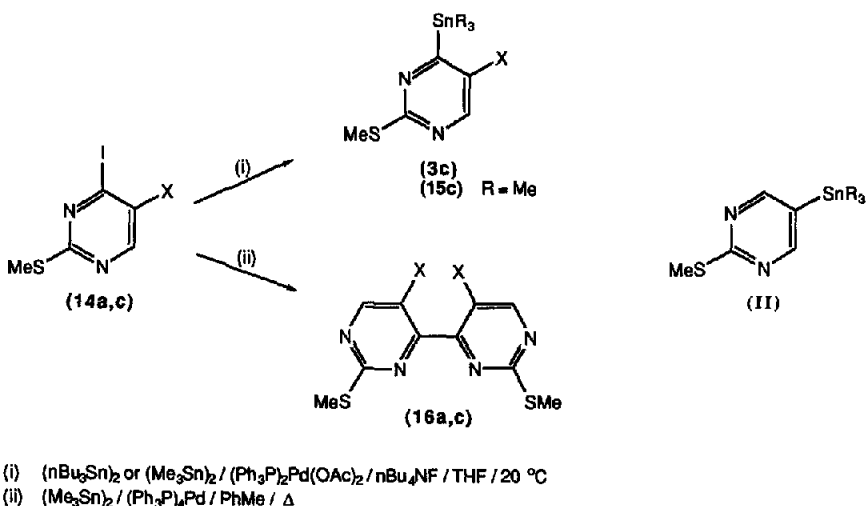
From our studies of organometallic adducts with π -electron deficient systems we know that the 2-pyrimidinones are highly polarized. As a consequence, 4-carboxylic acid derivatives are easily decarboxylated, *e.g.* the decarboxylation of the acid (7a) in anisole as solvent is carried out at 45 °C (Scheme 2).⁹ The tin esters (9a) and (10a) were therefore prepared; bis(*tri-n*-butyltin) oxide was used. Decarboxylation with the formation of the 4-stannyl derivatives (11a) and (12a) occurred readily on heating the tin esters in anisole.



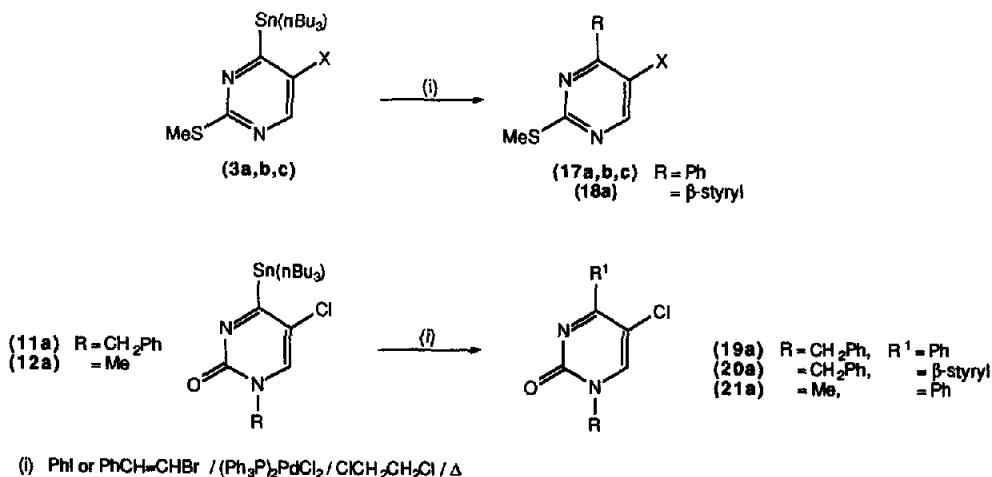
Scheme 3

Organotin-lithium, sodium, magnesium or copper reagents can be used for stannylation by nucleophilic substitution.^{10,11} The reaction between the 4-chloro derivatives (13) and the organotin-lithium or copper reagents, however, was unsatisfactory. The chlorine in the activated 4-position was therefore exchanged for an iodide substituent by treating compounds (13) with hydroiodic acid. The stannyl-copper reagent was the better reagent for the stannylation reactions of the 4-iodo derivatives (14). The reagent was prepared from tri-*n*-butylstannane which was lithiated,¹² and treated with copper iodide.¹³ This reaction may not be a simple nucleophilic substitution, however, since the bromine in the benzenoid 5-position in the 5-bromo-2-methylthiopyrimidine isomer is readily displaced by a stannyl group (II; Scheme 3) in reactions with trimethyl- or tri-*n*-butyltin-lithium or copper.¹⁴ We have previously reported the preparation of 5-stannylated pyrimidines by lithiation of the bromide (-90 °C) and quenching the lithiated species by the addition of organostannyl halides; manipulations of the 2-substituents yield 5-stannyl-2(1*H*)-pyrimidinones which can be *N*-alkylated (I $\rightarrow$ III; Scheme 3).⁴

Palladium-catalyzed coupling of hexa-alkylditin with aryl halides provides a convenient method for the synthesis of aryltin derivatives.¹⁵ Stannylation in the pyrimidine 4-position (Scheme 4) can also be effected using hexamethyl- or hexa-*n*-butyl-ditin in the presence of 1-2 molar equivalents of fluoride ions. Several palladium catalysts were tried. The best catalyst was bis(triphenylphosphine)palladium(II) diacetate. The stannylation, however, is accompanied by various amounts of bipyrimidine which is formed by reductive coupling. Under our best conditions only small amounts of this product was formed, and it is readily removed during the work up. If the stannylation is run in the absence of fluoride ions and Pd(0)

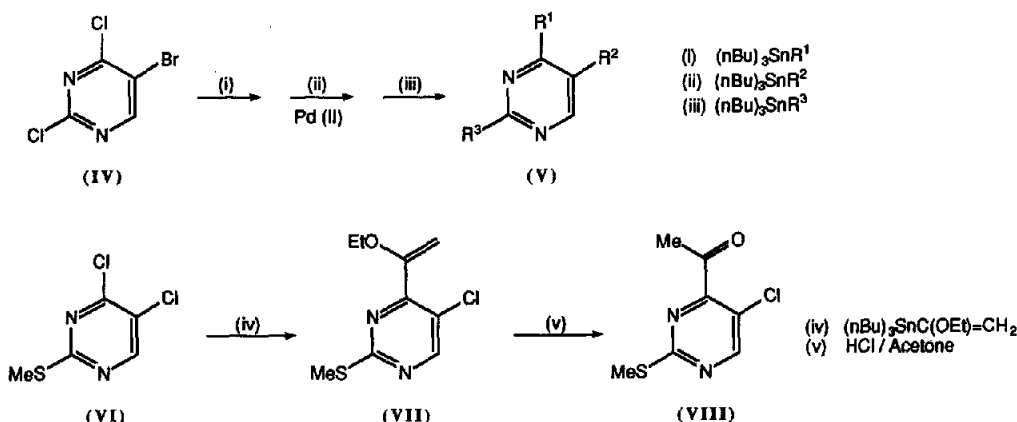
**Scheme 4**

catalysis, the product is the reductively coupled bipyrimidine (16). In the benzenoid 5-bromo derivative (I; Scheme 3) stannylation by hexa-*n*-butylditin also requires the presence of fluoride ions, and the best catalysts in this case were the Pd(II) complex with dibenzylideneacetone and the π -allylpalladium chloride complex; reductive coupling was not important.¹⁴

**Scheme 5**

The cross-coupling reactions with the stannylated pyrimidines were carried out with Pd(II)-catalysis. The 2-methylthio-4-stannylpyrimidines (3) were coupled with iodobenzene and β -bromostyrene. It should be noted that the 5-bromo derivative (3b) could be coupled with iodobenzene without significant interference from the bromo substituent. Coupling reactions with the 2-methylsulfonyl

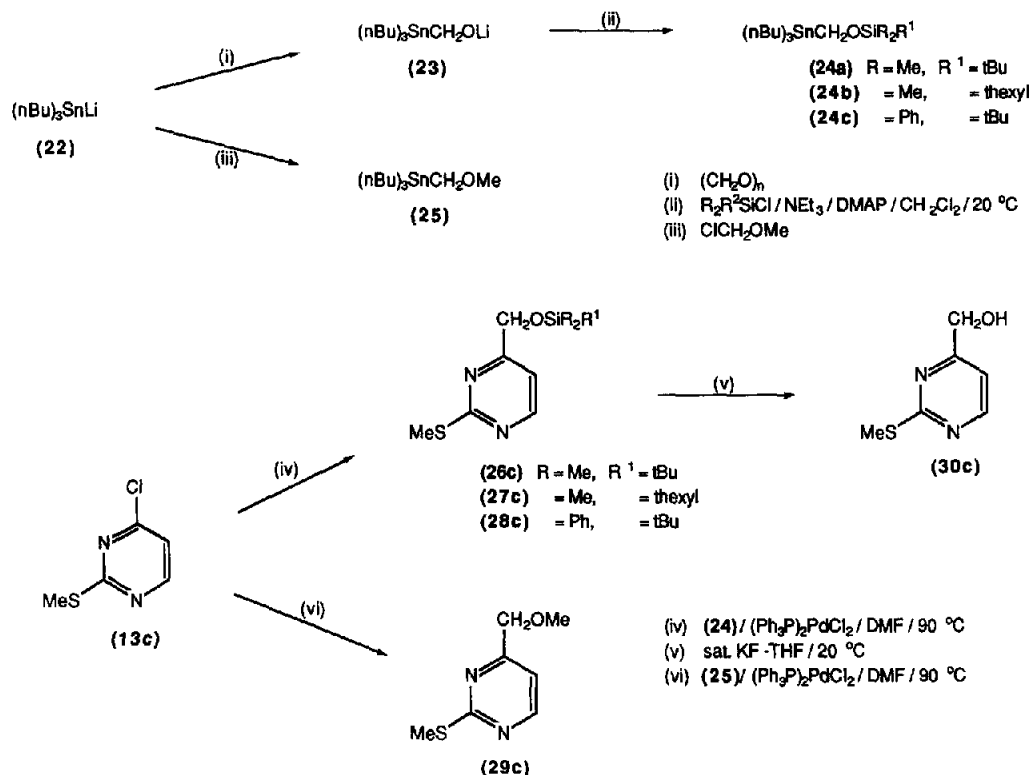
derivatives (6b) and (6c), however, lead to heterogenous products. In contrast, the isomeric 2-sulfonyl-5-stannylpyrimidines undergo efficient coupling under similar conditions.⁴ The 4-stannyl-2(1*H*)-pyrimidinones (11a) and (12a) are also readily coupled under the influence of Pd(II) catalysts. The products (19a)-(21a) contain a new 4-carbon substituent (Scheme 5).



Scheme 6

In coupling reactions between aryl halides and organostannyl reagents the arenes must generally be bromo or iodo derivatives for the coupling to occur;² replacement of a chlorine substituent requires the presence of a strongly electron withdrawing group in an activating position. In the π -electron deficient heteroaromatic systems chlorines are readily introduced into the activated positions by well established procedures. The corresponding bromo or iodo derivatives, however, are generally less readily available, and they are often prepared by halogen exchange reactions from the chlorides *e. g.* as in the conversion of the chlorides (13) to the iodides (14) (Scheme 3). This lead us to investigate reactivities of chloropyrimidines towards palladium-catalyzed cross-coupling reactions, and it has been found that the chlorines in activated pyrimidine positions can be replaced by carbon substituents using organotin reagents and palladium catalysis.⁵ The 4(6)-position in pyrimidine is more reactive than the 2-position, and regiospecific coupling can be achieved (Scheme 6). A bromine or iodine is required for coupling to take place in the benzenoid 5-position. Sequential substitution in 5-bromo-2,4-dichloropyrimidine gave the order of reactivity 4-Cl > 5-Br > 2-Cl.⁵ This methodology was used to introduce acyl functions into pyrimidines; α -ethoxyethenylpyrimidines were formed by the coupling procedure from α -stannylated vinyl ether, and the products were hydrolyzed to the acyl derivatives.⁵ In a continuation of the work on the introduction of functionalized carbon substituents, we have found that the hydroxymethyl group can be introduced by way of stannylmethyl silyl ethers (Scheme 7).

Direct hydroxymethylation of bromobenzenes to benzylic alcohols is reported using hydroxymethyl-tri-*n*-butyltin and Pd(0) catalysis; the reaction failed in the presence of electron withdrawing groups unless the hydroxyl group of the reagent was protected as the trimethylsilyl ether.¹⁶ We were looking for a protecting group which survives the reaction conditions and is not cleaved by the aqueous solution of fluoride ions which is added to the reaction mixture in order to precipitate the organotin co-product as the insoluble organotin fluoride during the work up of the reaction. For this purpose, *tert*-butyldimethylsilyl-, dimethylhexylsilyl- and *tert*-butyldiphenylsilyl-oxymethyl(tri-*n*-butyl)tin (24) have been prepared and studied in palladium catalyzed reactions with the 4-chloropyrimidine (13c; Scheme 7). The silylated hydroxymethyl tin reagents were prepared from tri-*n*-butyltin-lithium which was hydroxymethylated by treatment with paraformaldehyde,¹⁷ and reacted



Scheme 7

further with the appropriate silyl halide to form the product (24). For a comparison of reactivities, the ether reagent methoxymethyl(tri-*n*-butyl)tin was prepared from the lithiated organotin (22) by reaction with chloromethyl methyl ether.¹⁸

No coupling reaction was seen when tetrakis(triisopropylphosphite)palladium was tried as catalyst. The reaction proceeds, however, with Pd(II) catalysis. A series of complexes were tried. The best catalyst was the bistrisphenylphosphine complex. DMF and 1,2-dichloroethane were the best solvents. The reaction is slow because the group to be transferred is bonded to the tin through an sp^3 hybridized carbon.¹⁹ The methyl and silyl ethers show similar reactivities. The silyl ethers (26c-28c) are stable, but the silyl groups are readily cleaved when a solution in THF is treated with tetra-*n*-butylammonium fluoride whereby the 4-hydroxymethylthiopyrimidine (30c) is formed in high yield.

EXPERIMENTAL

The 1H NMR spectra were recorded at 300 MHz unless otherwise specified, the ^{13}C NMR spectra at 75 MHz. The MS spectra were recorded at 70 eV and are presented as m/z (% rel. int.). Isobutane was used for chemical ionization (CI) unless otherwise specified.

THF for use in the organometallic reactions was dried by reflux and distillation over metallic sodium-benzophenone.

Tri-*n*-butylstannyl 5-chloro-2-methylthiopyrimidine-4-carboxylate (2a). A solution of 5-chloro-2-methylthiopyrimidine-4-carboxylic acid²⁰ (0.50 g, 2.5 mmol) and bis(tri-*n*-butyltin) oxide (0.63

ml, 1.3 mmol) in dry benzene (25 ml) was heated for 3 h under nitrogen and azeotropic conditions using a Dean-Stark apparatus. The solvent was then distilled off and the residual material triturated with light petroleum. The residue was a white solid; yield 1.00 g (81%), m.p. 82 °C. (Found: C, 43.91; H, 6.43. Calc. for $C_{18}H_{31}ClN_2O_2SSn$: C, 43.79; H, 6.32%). IR (CHCl₃): 1660 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 0.8-1.6 (Bu), 2.49 (MeS), 8.67 (H-6). ¹³C NMR (DMSO-*d*₆): δ 13.7-27.7 (Bu), 13.9 (MeS), 120.4 (C-5), 156.8 (C-6), 161.1, 165.8 and 169 (CO₂, C-2 and C-4). MS (CI): 500/499/497/496/495/494/493/492/491 (7/15/32/21/75/31/54/19/27, *M*+1), 441(15), 439(32), 438 (19), 437(76), 436(30), 435(55), 434(19), 433(27), 295(16), 293(15), 292(13), 291(100), 290(35), 289(76), 283(30), 287(43).

Tri-*n*-butylstannyl 5-bromo-2-methylthiopyrimidine-4-carboxylate (2b). Compound (2b) was prepared as described above from 5-bromo-2-methylthiopyrimidine-4-carboxylic acid²⁰ in 97% yield, m.p. 94-95 °C. (Found: C, 40.06; H, 5.73. Calc. for $C_{18}H_{31}BrN_2O_2SSn$: C, 40.17; H, 5.80%). IR (CDCl₃): 1670 cm⁻¹. ¹H NMR (CDCl₃): δ 0.9-1.7 (Bu), 2.54 (MeS), 8.61 (H-6). ¹³C NMR (CDCl₃): δ 13.5-27.5 (Bu), 14.3 (MeS), 110.2 (C-5), 159.4 and 159.8 (C-4, C-6), 167.8 and 171.2 (CO₂, C-2). MS (CI): 545/543/541/540/539/538/537/536/535 (1/2/9/4/13/5/8/1, *M*+1), 487 (2), 485 (3), 484 (2), 483 (13), 482 (5), 481 (20), 480 (6), 479 (13), 478 (29), 477 (5), 295 (15), 294 (1), 293 (15), 292 (12), 291 (100), 290 (33), 289 (74), 288 (27), 287 (40).

5-Chloro-2-methylthio-4-tri-*n*-butylstannylpyrimidine (3a) by decarboxylation. Method (i): A mixture of tri-*n*-butylstannyl 5-chloro-methylthiopyrimidine-4-carboxylate (0.50 g, 1.01 mmol) and bis(acetonitrile)palladium(II) dichloride (17.5 mg, 0.067 mmol) in anisole (10 ml) under nitrogen was heated under reflux until the starting material was consumed (*ca.* 9 h). The solvent was then distilled off at reduced pressure and the residual material chromatographed on dry-packed neutral alumina using 2% EtOAc in light petroleum; yield 0.33 g (73%) of an oily material which was distilled, b.p. 110 °C/0.05 mmHg. (Found: C, 45.53; H, 7.00. Calc. for $C_{17}C_3H_{31}ClN_2SSn$: C, 45.40; H, 6.94%). ¹H NMR (CDCl₃): δ 0.8-1.5 (Bu), 2.48 (MeS), 8.16 (H-6, *J*_{Sn,H-6} 18 Hz). ¹³C NMR (CDCl₃): δ 10.0-28.7 (Bu), 13.7 (MeS), 136.3 (C-5), 151.7 (C-6), 168.3 (C-4), 184.6 (C-2). MS (CI): 455/453/452/451/450/449/448/447 (2/5/3/11/4/8/2/5, *M*+1), 399(2), 398 (8), 397 (7), 396 (5), 395 (16), 394 (13), 393 (41), 391 (27), 390 (10), 389 (13), 127 (100), 95 (10), 81 (20).

Method (ii): Tri-*n*-butylstannyl 5-chloro-2-methylthiopyrimidine-4-carboxylate (0.10 g, 2.0 mmol) in a round-bottom flask at 10 mmHg was heated at 190-200 °C for 3 h. The product was isolated by chromatography as described above; yield 35 mg (39%).

5-Chloro-2-methylthio-4-tri-*n*-butylstannylpyrimidine (3a) from tri-*n*-butyltin-copper. A solution of 5-chloro-4-iodo-2-methylthiopyrimidine (0.67 g, 2.6 mmol) in dry THF (5 ml) was added dropwise with stirring to a solution of tri-*n*-butyltin-copper¹³ (5 mmol) in dry THF (10 ml) under nitrogen at -78 °C, the mixture stirred at -78 °C for 6 h, at ambient temperature overnight, filtered, the filtrate evaporated and the oily residue chromatographed on dry-packed neutral alumina using 2% EtOAc in light petroleum; yield 0.56 g (52%). Physical data for this compound have been described above.

5-Bromo-2-methylthio-4-tri-*n*-butylstannylpyrimidine (3b) by decarboxylation. Method (i): Compound (3b) was prepared as described above from tri-*n*-butylstannyl 5-bromo-2-methylthiopyrimidine-4-carboxylate. The crude product was purified by chromatography on dry-packed neutral alumina using 5% EtOAc in light petroleum; yield 70% of a colourless material. (Found: C, 41.64; H, 6.56. Calc. for $C_{17}H_{31}BrN_2SSn$: C, 41.32, H, 6.32%). ¹H NMR (CDCl₃): δ 0.8-1.6 (Bu), 2.55 (MeS), 8.32 (H-6, *J*_{Sn,H-6} 18 Hz). ¹³C NMR (CDCl₃): δ 11.1-28.8 (Bu), 14.3 (MeS), 127.3 (C-5), 154.1 (C-6), 168.8 (C-4), 187.5 (C-2). MS (CI): 499/498/497/496/495/494/493/492/491 (10/7/45/18/72/21/35/8/15, *M*+1), 443 (3), 441 (13), 440 (2), 439 (30), 438 (16), 437 (50), 436 (17), 435 (31), 434 (5), 433 (7), 129 (5), 127 (100), 126 (15).

Method (ii): The yield was 40%.

2-Methylthio-4-tri-*n*-butylstannylpyrimidine (3c) from tri-*n*-butyltin-copper. Compound (3c)

was prepared as described above from 4-iodo-2-methylthiopyrimidine. The crude product was chromatographed on dry-packed neutral alumina using EtOAc:light petroleum 1:9. The analytical specimen of the oily product was distilled, b.p.112 °C/0.01 mmHg, yield 41%. (Found: C, 49.22; H, 7.65. Calc. for $C_{17}H_{32}N_2SSn$: C, 49.18; H, 7.76%). 1H NMR ($CDCl_3$): δ 0.9-1.5 (Bu), 2.52 (MeS), 7.04 (H-5, J 5 Hz, $J_{Sn,H-5}$ 18 Hz), 8.20 (H-6, J 4 Hz, $J_{Sn,H-6}$ 15 Hz). ^{13}C NMR ($CDCl_3$): δ 9.8-28.7 (Bu), 13.8 (MeS), 125.1 (C-5), 153.6 (C-6), 170.9 (C-4), 185.6 (C-2). MS (CI): 421/419/418/417/416/415/414/413 (8/9/12/70/27/56/17/22, $M+1$), 360 (8), 359 (30), 358 (9), 357 (16), 365 (5), 355 (6), 295 (8), 293 (7), 292 (7), 291 (72), 290 (20), 289 (56), 288 (20), 287 (21), 85 (100), 79 (76).

2-Methylthio-4-tri-*n*-butylstannylpyrimidine (3c) from hexa-*n*-butylditin. A mixture of 4-iodo-2-methylthiopyrimidine (0.5 g, 1.9 mmol), hexa-*n*-butylditin (2.3 g, 3.9 mmol), bis(triphenylphosphine)palladium(II) diacetate (13 mg, 0.059 mmol) and tetra-*n*-butylammonium fluoride (0.5 M in THF; 11.9 ml, 5.9 mmol) in dry THF (3 ml) under nitrogen was stirred at ambient temperature for 6 h. The solvent was then evaporated and the residual material was chromatographed on dry-packed neutral alumina using 2% EtOAc in light petroleum. The products eluted from the column were the title compound (3c) 0.37 g (46%), 2,2'-dimethylthio-4,4'-dipyrimidine (16c) 0.13 g (20%) and 2-methylthiopyrimidine 0.04 g (15%). Physical data for the compounds (3c) and (16c) are described elsewhere.

Tri-*n*-butylstannyl 5-bromo-2-methylsulfonylpyrimidine-4-carboxylate (5b). A solution of 5-bromo-2-methylsulfonylpyrimidine-4-carboxylic acid²⁰ (1.18 g, 4.2 mmol) and bis(tri-*n*-butyltin) oxide (1.07 ml, 2.1 mmol) in dry toluene (25 ml) under nitrogen was heated for 3 h under reflux and azeotropic conditions using a Dean-Stark apparatus. The solvent was then distilled off and the residual material triturated with light petroleum. The product was a white solid; yield 2.00 g (84%), m.p. 90-92 °C. 1H NMR (60 MHz $CDCl_3$): δ 0.8-1.8 (Bu), 3.30 (MeSO₂), 9.00 (H-6).

5-Bromo-2-methylsulfonyl-4-tri-*n*-butylstannylpyrimidine (6b) by oxidation.. Compound (6b) was prepared from 5-bromo-2-methylthio-4-tri-*n*-butylstannylpyrimidine and *m*-chloroperbenzoic acid by the procedure described for compound (6c). The crude product was purified by flash chromatography on silica gel using hexane:ethyl acetate 8:1; yield 80% of an oily material. 1H NMR (60 MHz $CDCl_3$): δ 1.8-2.2 (Bu), 3.20 (MeSO₂), 8.60 (H-6, $J_{Sn,H-6}$ 14 Hz).

5-Bromo-2-methylsulfonyl-4-tri-*n*-butylstannylpyrimidine (6b) by decarboxylation. Tri-*n*-butylstannyl 5-bromo-2-methylsulfonylpyrimidine-4-carboxylate (113 mg, 0.20 mmol) in a round bottom flask at 12 mmHg was heated at 225 °C for 10 min. The reaction mixture was then cooled, extracted with dichloromethane, the solution evaporated and the residual material subjected to flash chromatography on silica gel using hexane:ethyl acetate; yield 22 mg (21%).

2-Methylsulfonyl-4-tri-*n*-butylstannylpyrimidine (6c). A solution of 2-methylthio-4-tri-*n*-butylstannylpyrimidine (0.3 g, 0.7 mmol) and *m*-chloroperbenzoic acid (0.34 g, 2 mmol) in dichloromethane (40 ml) was stirred at 0 °C for 24 h. The mixture was shaken with a saturated sodium bisulphite solution (2x20 ml), with a saturated sodium carbonate solution (2x25 ml), the solution dried (MgSO₄), evaporated and the product chromatographed on dry-packed neutral alumina using EtOAc:light petroleum 1:5; yield 0.3 g (96%). (Found: C, 45.30; H, 7.70. Calc. for $C_{17}H_{32}N_2O_2SSn$: C, 45.65; H, 7.21%). 1H NMR ($CDCl_3$): δ 0.9-1.7 (Bu), 3.36 (MeSO₂), 7.65 (H-5, J 5 Hz, $J_{Sn,H-5}$ 14 Hz), 8.67 (H-6, J 5 Hz $J_{Sn,H-6}$ 14 Hz). ^{13}C NMR ($CDCl_3$): δ 16.2-28.7 (Bu), 38.7 (MeSO₂), 132.3 (C-5), 154.3 (C-6), 165.1 (C-4), 189.5 (C-2).

Tri-*n*-butylstannyl 1-benzyl-5-chloro-2-oxo-1,2-dihydropyrimidine-4-carboxylate (9a). A mixture of 1-benzyl-5-chloro-2-oxo-1,2-dihydropyrimidine-4-carboxylic acid⁹ (0.60 g, 1.8 mmol) and bis(tri-*n*-butyltin) oxide (0.45 ml, 0.9 mmol) in dry benzene (20 ml) was heated under reflux for 3 h with azeotropic removal of water using a Dean-Stark apparatus, the solvent evaporated and the residue

trituated with light petroleum; yield 0.76 g (72%), m.p. 104–106 °C. (Found: C, 51.97; H, 6.32. Calc. for $C_{24}H_{35}ClN_2O_3Sn$: C, 52.05; H, 6.37%). IR (CHCl₃): 1670 cm⁻¹. ¹H NMR (CDCl₃): δ 0.9–1.7 (Bu), 5.08 (CH₂Ph), 7.2–7.4 (Ph), 7.62 (H-6). ¹³C NMR (CDCl₃): δ 13.6–27.6 (Bu), 54.0 (CH₂Ph), 107.3 (C-5), 128.6/128.8/129.1/133.7 (Ph), 145.5 (C-6), 154.2 (C-4), 166.2 and 166.4 (CO₂, C-2). MS (CI): 553/551 (2/2, *M*+1), 515 (6), 514 (4), 513 (16), 512 (9), 511 (24), 510 (10), 509 (12), 508 (4), 507 (3), 295 (7), 293 (6), 292 (7), 291 (54), 290 (19), 289 (41), 288 (16), 287 (25), 285 (3), 283 (4), 93 (30), 92 (33), 90 (100).

Tri-*n*-butylstannyl 5-chloro-1-methyl-2-oxo-1,2-dihydropyrimidine-4-carboxylate (10a). Compound (10a) was prepared as described above from 5-chloro-1-methyl-2-oxo-1,2-dihydropyrimidine-4-carboxylic acid⁹; yield 72%, m.p. 200 °C. (Found: C, 44.75; H, 6.34. Calc. for $C_{18}H_{31}ClN_2O_3Sn$: C, 45.20; H, 6.54%). IR (CHCl₃): 1670, 1620 cm⁻¹. ¹H NMR (CDCl₃): δ 0.9–1.7 (Bu), 3.58 (MeN), 7.80 (H-6). ¹³C NMR (CDCl₃): δ 13.4–27.5 (Bu), 39.2 (MeN), 107.1 (C-5), 147.2 (C-6), 154.7 (C-4), 166.3 and 166.7 (CO₂, C-2). MS (CI): 484/482/480/479/478/477/476/475/474 (3/18/42/27/100/43/76/28/42, *M*+1), 438 (15), 436 (27), 435 (63), 434 (26), 433 (45), 431 (20), 418 (28), 376 (18), 290 (53).

1-Benzyl-5-chloro-4-tri-*n*-butylstannyl-2(1H)-pyrimidinone (11a). A solution of tri-*n*-butylstannyl 1-benzyl-5-chloro-2-oxo-1,2-dihydro pyrimidine-4-carboxylate (0.50 g, 1.0 mmol) in dry anisole (25 ml) under nitrogen was heated under reflux for 45 min when TLC monitoring showed that all the starting material had reacted. The solvent was then removed at reduced pressure, and the residue was chromatographed on dry-packed basic silica gel using EtOAc; yield 0.30 g (66%). The analytical specimen was distilled, b.p. 110 °C/0.05 mmHg. (Found: C, 54.01; H, 6.81. Calc. for $C_{32}H_{35}ClN_2OSn$: C, 54.19; H, 6.92%). IR (CDCl₃): 1640, 1590 cm⁻¹. ¹H NMR (CDCl₃): δ 0.9–1.6 (Bu), 5.02 (CH₂Ph), 7.35 (Ph), 7.48 (H-6 *J*_{Sn,H-6} 15 Hz). ¹³C NMR (CDCl₃): δ 11.2–28.8 (Bu), 53.9 (CH₂Ph), 119.9 (C-5), 128.7/128.8/129.1/134.7 (Ph), 139.1 (C-6), 153.3 (C-4), 200.7 (C-2). MS (CI): 515/514/513/512/511/509/507/506/505/504/503 (0.4/0.1/0.9/0.7/3/2/0.9/0.6/0.1/0.3, *M*+1), 295 (11), 293 (10), 292 (8), 291 (64), 289 (22), 288 (49), 287 (27), 269 (22), 267 (17), 220 (100), 203 (19), 91 (88).

5-Chloro-1-methyl-4-tri-*n*-butylstannyl-2(1H)-pyrimidinone (12a). Compound (12a) was prepared as described above from tri-*n*-butylstannyl 5-chloro-1-methyl-2-oxo-1,2-dihydro-pyrimidine-4-carboxylate. The product was purified on neutral alumina using EtOAc:light petroleum 1:1; yield 71% of a non-crystalline material. (Found: C, 47.09; H, 7.25. Calc. for $C_{17}H_{31}ClN_2OSn$: C, 47.08; H, 7.20%). ¹H NMR (CDCl₃): δ 0.9–1.7 (Bu), 3.51 (MeN); 7.49 (H-6 *J*_{Sn,H-6} 15 Hz). ¹³C NMR (CDCl₃): δ 11.1–28.7 (Bu), 39.1 (MeN), 119.4 (C-5), 140.3 (C-6), 153.6 (C-4), 200.0 (C-2). MS (CI): 441/439/438/437/435/434/433/432/431 (3/5/3/12/17/3/10/2/4, *M*+1), 295 (4), 293 (1), 292 (4), 291 (22), 290 (10), 289 (15), 288 (7), 287 (9), 285 (2), 153 (8), 151 (14), 150 (6), 149 (11), 148 (7), 147 (37), 146 (9), 145 (67), 71 (100).

4-Iodo-2-methylthiopyrimidine (14c). 4-Chloro-2-methylthiopyrimidine²¹ (8.99 g, 5.6 mmol) was added to hydroiodic acid (57%; 45 ml), the mixture stirred at ambient temperature for 48 h, filtered, the solid dissolved in water (50 ml) and the pH brought to 8 by the addition of solid sodium bicarbonate. The mixture was extracted with chloroform (2x25 ml), the chloroform solution washed with sodium sulphite (2x25 ml), with water (2x25 ml), dried (MgSO₄), evaporated and the residue recrystallized from light petroleum; yield 10.77 g (76%), m.p. 52–53 °C. (Found: C, 24.02; H, 2.07. Calc. for $C_5H_5IN_2S$: C, 23.82; H, 1.98%). ¹H NMR (CDCl₃): δ 2.53 (MeS), 7.45 (H-5, d, *J* 4.5 Hz), 8.09 (H-6, d, *J* 4.5 Hz). ¹³C NMR (CDCl₃): δ 14.3 (MeS), 127.2 (C-5), 129 (C-4), 155.7 (C-6), 173.1 (C-2). MS: 252 (100, *M*), 206 (7), 127 (17), 125 (57), 110 (14), (79 (13)).

2-Methylthio-4-trimethylstannylpyrimidine (15c). Compound (15c) was prepared as described above from hexamethylditin in 54% yield. (Found: C, 33.04; H, 4.86. Calc. for $C_8H_{14}N_2SSn$: C, 33.24; H, 4.88%). ¹H NMR (CDCl₃): δ 0.26 (Me), 2.56 (MeS), 7.11 (H-5, *J* 5 Hz, *J*_{Sn,H-5} 20 Hz), 8.27 (H-6, *J* 5 Hz, *J*_{Sn,H-6} 19 Hz). ¹³C NMR (CDCl₃): δ 0.2–31.7 (Me), 13.2 (Me), 22.4 (MeS), 124.3 (C-5), 153.4 (C-6), 171.1 (C-4), 184.0 (C-2). MS (CI): 295/294/293/292/291/290/289/288/287/285 (15/19/10/

100/36/75/28/42/2, *M*+1), 278 (3), 277 (3), 276 (1), 275 (12), 274 (4), 273 (9), 271 (6), 250 (7), 143 (17).

2,2'-Dimethylthio-5,5'-dichloro-4,4'-bipyrimidine (16a). A mixture of 5-chloro-4-iodo-2-methylthiopyrimidine²² (0.76 g, 3.0 mmol), hexamethylditin (1.76 g, 3.0 mmol) and tetrakis(triphenylphosphine)palladium (23 mg, 0.0195 mmol) in toluene (8 ml) was heated under reflux for 20 h. The cold mixture was filtered, the filtrate evaporated at reduced pressure and the residue chromatographed on dry-packed alumina using EtOAc:light petroleum 1:20; yield 56%. (Found: C, 37.50; H, 2.42. Calc. for C₁₀H₈Cl₂N₄S₂: C 37.62; H 2.52%). ¹H NMR (CDCl₃): δ 2.54 (MeS), 8.46 (H-6). ¹³C NMR (CDCl₃): δ 14.1 (MeS), 126.1 (C-5), 155.2 (C-6), 168.4 (C-4), 170.4 (C-2).

2,2'-Dimethylthio-4,4'-bipyrimidine (16c). Compound (16c) was prepared as described above from 4-iodo-2-methylthiopyrimidine and the reaction mixture worked up in the same way; yield 38%, m.p. 184–185 °C. (Found: C, 48.09; H, 3.99. Calc. for C₁₀H₁₀N₄S₂: C, 47.97; H, 3.99%). ¹H NMR (CDCl₃): δ 2.63 (MeS), 8.03 (H-5, d, *J* 4 Hz), 8.71 (H-6, d, *J* 4 Hz). ¹³C NMR (CDCl₃): δ 14.4 (MeS), 112.9 (C-5), 159.3 (C-6), 161.2 (C-4), 173.4 (C-2). MS: 250 (100, *M*), 220 (36), 177 (20), 162 (6), 144 (4), 130 (7), 110 (8).

5-Chloro-2-methylthio-4-phenylpyrimidine (17a). A mixture of 5-chloro-2-methylthio-4-tri-*n*-butylstannylpyrimidine (1.00 g, 2.2 mmol), iodobenzene (0.50 g, 2.67 mmol) and bis(triphenylphosphine)palladium(II) dichloride (37 mg, 0.052 mmol) in 1,2-dichloroethane (25 ml) under nitrogen was heated under reflux for 4 h. A saturated solution of potassium fluoride in methanol (20 ml) was added and the mixture stirred at ambient temperature for 1 h, filtered, the filtrate washed with water (3x25 ml), dried (MgSO₄), evaporated and the residual material chromatographed on dry neutral alumina using EtOAc:light petroleum 1:1; yield 0.30 g (65%), m.p. 70 °C.^{3a}

5-Bromo-2-methylthio-4-phenylpyrimidine (17b). Compound (17b) was obtained as described above from 5-bromo-2-methylthio-4-tri-*n*-butylstannylpyrimidine. The reaction mixture was heated under reflux for 4 h in DMF; yield 55%, m.p. 88–90 °C. (Found: C, 46.76; H, 3.38. Calc. for C₁₁H₉BrN₂S: C, 46.69; H, 3.22%). ¹H NMR (CDCl₃): δ 2.65 (MeS), 7.2–7.5 (Ph), 8.51 (H-6). ¹³C NMR (CDCl₃): δ 14.1 (MeS), 127.6–137.2 (C-5, Ph), 158 (C-6), 163.3 (C-4), 171.0 (C-2). MS: 282/280 (94/100, *M*), 236 (16), 234 (12), 156 (61), 77 (19).

2-Methylthio-4-phenylpyrimidine (17c). Compound (17c) was prepared as described above from 2-methylthio-4-tri-*n*-butylstannylpyrimidine. The crude product was purified by chromatography on dry-packed neutral alumina using EtOAc:light petroleum 1:9; yield 63%, m.p. 77–78 °C. (Found: C, 65.12; H, 4.91. Calc. for C₁₁H₁₀N₂S: C, 65.31; H, 4.98%). ¹H NMR (CDCl₃): δ 2.63 (MeS), 7.35 (H-5, d, *J* 6 Hz), 7.5–8.1 (Ph), 8.52 (H-6, d, *J* 6 Hz). ¹³C NMR (CDCl₃): δ 14.0 (MeS), 111.6 (C-5), 126.9/128.6/130.9/136.1 (Ph), 157.4 (C-6), 163.5 (C-4), 172.6 (C-2). MS: 202 (100, *M*), 188 (8), 176 (28), 162 (6), 144 (12), 104 (11), 77 (16).

5-Chloro-2-methylthio-4-β-trans-styrylpyrimidine (18a). A mixture of 5-chloro-2-methylthio-4-tri-*n*-butylstannylpyrimidine (0.50 g, 1.1 mmol), β-bromostyrene (0.26 g, 1.5 mmol) and bis(triphenylphosphine)palladium(II) dichloride (22 mg, 0.031 mmol) in DMF (20 ml) under nitrogen was heated under reflux for 3 h. A saturated solution of potassium fluoride in methanol (25 ml) was added to the cold reaction mixture and the mixture stirred at ambient temperature for 1 h, filtered, the filtrate washed with water (2x25 ml), dried (MgSO₄), evaporated at reduced pressure and the residue chromatographed on dry-packed neutral alumina using EtOAc:light petroleum 1:4; yield 0.30 g (73%); m.p. 82 °C.^{3a}

1-Benzyl-5-chloro-4-phenyl-2(1H)-pyrimidinone (19a). A mixture of 1-benzyl-5-chloro-4-tri-*n*-butylstannyl-2(1H)-pyrimidinone (0.3 g, 0.59 mmol), iodobenzene (0.12 g, 0.59 mmol) and

bis(triphenylphosphine)palladium(II) dichloride (33 mg, 0.04 mmol) in dry 1,2-dichloroethane (15 ml) under nitrogen was heated under reflux for 5 h. A saturated solution of potassium fluoride in methanol (15 ml) was added, the mixture stirred at ambient temperature for 1 h, filtered, the filtrate washed with water (2x20 ml), dried (MgSO₄), evaporated and the residual material chromatographed on dry-packed neutral alumina using EtOAc; yield 1.20 g, (69%), m.p. 158-159 °C. **1a**

1-Benzyl-5-chloro-4-β-trans-styryl-2(1H)-pyrimidinone (20a). Compound (**20a**) was prepared as described above from 1-benzyl-5-chloro-4-tri-*n*-butylstannyl-2(1H)-pyrimidinone, β-*trans*-bromostyrene and the Pd(II) catalyst by heating a solution in 1,2-dichloroethane under reflux for 4 h. The product was purified on dry-packed neutral alumina using EtOAc:light petroleum 1:1; yield 67%, m.p. 109 °C (EtOH). (Found: C, 69.02; H, 4.52. Calc. for C₁₉H₁₅ClN₂O: C, 70.09; H 4.68%). ¹H NMR (CDCl₃): δ 5.11 (CH₂), 7.34 and 8.23 (CH=CH, *J* 13 Hz), 7.3-7.7 (2xPh), 7.59 (H-6). ¹³C NMR (CDCl₃): δ 53.6 (CH₂), 110.9 (C-5), 119.3 and 144.6 (CH=CH, d), 128.6/128.8/ 128.9/129.9/130.5/134.6/135.2 (2xPh), 143.2 (C-6), 154.9 (C-4), 166.1 (C-2). MS: 324/322 (6/17, *M*), 247 (4), 245 (12), 233 (2), 231 (6), 91 (100), 65 (10).

5-Chloro-1-methyl-4-phenyl-2(1H)-pyrimidinone (21a). Compound (**21a**) was prepared as above from 5-chloro-1-methyl-4-tri-*n*-butylstannyl-2(1H)-pyrimidinone in 65% yield, m.p. 200 °C. (Found: C, 59.86; H, 4.02. Calc. for C₁₁H₉ClN₂O: C, 59.88; H, 4.11%). ¹H NMR (CDCl₃): δ 33.61 (MeN), 7.4-7.8 (Ph), 7.99 (H-6). ¹³C NMR (CDCl₃): δ 38.6 (MeN), 127.8/129.1/130.8 (Ph), 135.1 (C-5), 147.0 (C-6), 147.0 (C-4), 154.8 (C-4), 171.7 (C-2). MS: 221/219 (34/100, *M*), 77 (4).

General procedure for the preparation of (silyloxymethyl)tri-*n*-butyltin compounds (24). *n*-Butyllithium in hexane (31.3 ml, 50 mmol) was added to a solution of dry isopropylamine (5.57 g, 55 mmol) in dry THF (100 ml) under nitrogen at 0 °C. After 15 min tri-*n*-butylstannane (13.0 ml, 50 mmol) was added dropwise, the solution stirred at 0 °C for 30 min, paraformaldehyde (1.55 g, 50 mmol) added, the mixture stirred at ambient temperature for 3 h, aqueous 1 M ammonium chloride solution added, stirred and the mixture extracted with diethyl ether. The washed and dried (MgSO₄) ether solution was evaporated and the residue dissolved in dichloromethane (100 ml). The silyl halide (55 mmol), triethylamine (6.07 g, 60 mmol) and 4-*N,N*-dimethylaminopyridine (0.24 g, 2 mmol) were added to the dichloromethane solution, and the resultant solution stirred at ambient temperature overnight. The solution was then washed with 1 M ammonium chloride solution (50 ml), dried (MgSO₄), evaporated and the product purified by flash chromatography on silica gel using pentane.

(tert-Butyldimethylsilyloxymethyl)tri-*n*-butyltin (24a). Compound (**24a**) was a colourless liquid, yield 68%. (Found: C, 52.62; H, 10.29. Calc. for C₁₉H₄₄OSiSn: C, 52.42; H, 10.19%). ¹H NMR (CDCl₃): δ 0.02 (Me₂Si), 0.8-1.6 (*n*Bu, *t*Bu), 3.90 (CH₂O). ¹³C NMR (CDCl₃): δ 6.1 (Me₂Si), 8.8/13.6/27.3/29.1 (*n*Bu), 18.2 (Me₃C), 25.9 (Me₃C), 52.8 (CH₂O). MS (CI-NH₃): 425 [(*M*+NH₄⁺)-Bu, 22], 424 (100), 423 (38), 422 (64), 420 (34), 409 (7), 408 (8), 407 (37), 406 (16), 405 (28), 404 (12), 403 (15), 310 (8), 309 (6), 308 (37), 307 (13), 306 (25), 305 (10), 304 (14).

(Thexyldimethylsilyloxymethyl)tri-*n*-butyltin (24b). Compound (**24b**) was a colourless oil, yield 79%. ¹H NMR (CDCl₃): δ 0.05 (Me₂Si), 0.8-1.7 (*n*Bu, *thexyl*), 3.85 (CH₂). ¹³C NMR (CDCl₃): δ -4.2 (Me₂Si), 8.8/13.6/ 18.5/20.3/25.1/27.3/29.1/34.2 (*n*Bu, *thexyl*), 52.3 (CH₂O). MS (CI-NH₃): 397 [(*M*+NH₄⁺)-Bu, 8], 396 (35), 395 (14), 394 (32), 393 (12), 392 (18), 381 (19), 380 (10), 379 (100), 378 (39), 377 (71), 376 (30), 375 (38), 309 (4), 308 (34), 307 (12), 306 (27), 305 (10), 304 (15).

(tert-Butyldiphenylsilyloxymethyl)tri-*n*-butyltin (24c). Compound (**24c**) was a colourless liquid, Yield 76%. ¹H NMR (CDCl₃): δ 0.8-1.6 (Bu), 1.03 (Me₃C), 3.94 (OCH₂), 7.3-7.8 (Ar). ¹³C NMR (CDCl₃): δ 8.8/13.6/ 19.2/26.8/27.4/29.1 (*n*Bu, *t*Bu), 54.4 (CH₂O), 127.4/129.3/133.7/135.7. MS (CI-NH₃): 519 [(*M*+NH₄⁺)-Bu, 2], 505 (20), 504 (27), 503 (100), 502 (47), 501 (76), 500 (36), 499 (44), 308 (6), 307 (2), 306 (4), 305(3), 304 (3).

General procedure for the preparation of 2-methylthio-4-silyloxymethylpyrimidines (26-28). A solution of the (silyloxymethyl)tri-*n*-butyltin reagent (7.80 mmol), 4-chloro-2-methylthiopyrimidine (0.96 g, 6.00 mmol) and bis(triphenylphosphine)palladium(II) dichloride (76 mg, 0.12 mmol) in dry DMF (6 ml) under nitrogen was stirred at 90 °C until black palladium was precipitated (12-24 h). Diethyl ether (100 ml) was then added, the mixture cooled to 0 °C and saturated aqueous potassium fluoride solution (10 ml) added. The mixture was stirred for 30 min before the phases were separated. The organic phase was washed with water (3x50 ml), dried (MgSO₄) and evaporated. The product was purified by flash chromatography on silica gel first using pentane and then pentane:ethyl acetate 10:1. The products were colourless liquids.

4-tert-Butyldimethylsilyloxymethyl-2-methylthiopyrimidine (26c). Compound (26c) was obtained in 53% yield. ¹H NMR (CDCl₃): δ 0.12 (Me₂Si), 0.96 (Me₃C), 2.55 (MeS), 4.71 (CH₂), 7.18 (H-5, d, *J* 5.1 Hz) 8.51 (H-6, d, *J* 5.1 Hz). ¹³C NMR (CDCl₃): δ -5.6 (Me₂Si), 13.6 (MeS), 18.1 (Me₃C), 25.7 (Me₃C), 64.9 (CH₂), 112.1, 157.4, 170.5, 171.5. MS (CI): 273 (9), 272 (20), 271 (100, *M*+1), 255 (2), 215 (8), 214 (4), 213 (93), 198 (2).

2-Methylthio-4-thexyldimethylsilyloxymethylpyrimidine (27c). Compound (27c) was obtained in 32% yield. ¹H NMR (CDCl₃): δ 0.16 (Me₂Si), 0.92 (Me₂CSi), 0.93 (Me₂CSi), 0.93 (Me₂CH, d, *J* 6.9 Hz), 1.68 (CHMe₂, dq, *J* 6.9 Hz), 4.69 (CH₂), 7.18 (H-5, d, *J* 5.1 Hz), 8.50 (H-6, d, *J* 5.1 Hz). ¹³C NMR (CDCl₃): δ -3.7 (Me₂Si), 13.7 (MeS), 18.3/20.1/25.1/34.0 (thexyl), 64.8 (CH₂), 112.1 (C-5), 157.3 (C-6), 170.5, 171.4. MS (CI): 301 (11), 300 (23), 299 (100, *M*+1), 283 (1), 215 (2), 214 (3), 213 (20), 141 (12).

4-tert-Butyldiphenylsilyloxymethyl-2-methylthiopyrimidine (28c). Compound (28c) was obtained in 64% yield. ¹H NMR (CDCl₃): δ 1.14 (Me₃C), 2.48 (MeS), 4.76 (CH₂), 7.3-7.7 (Ph, H-5), 8.53 (H-6, d, *J* 5.1 Hz). ¹³C NMR (CDCl₃): δ 13.7 (MeS), 19.1 (Me₃C), 26.6 (Me₃C), 65.6 (CH₂), 112.1 (C-5), 127.7/129.8/132.5/135.2 (Ph), 157.4 (C-6), 169.9, 171.5. MS (CI): 337 (100, *M*+1), 321 (2), 289 (2), 260 (2), 213 (27), 199 (8).

4-Methoxymethyl-2-methylthiopyrimidine (29c). Compound (29c) was prepared as described above from (methoxymethyl)tri-*n*-butyltin¹⁸ and 4-chloro-2-methylthiopyrimidine.²¹ The crude product was purified by flash chromatography on silica gel using pentane:ethyl acetate 3:1; yield 56%, colourless liquid. ¹H NMR (CDCl₃): δ 2.55 (MeS), 3.48 (MeO), 4.47 (CH₂), 7.11 (H-5, d, *J* 5.1 Hz), 8.50 (H-6, d, *J* 5.1 Hz). ¹³C NMR (CDCl₃): δ 13.8 (MeS), 73.9 (CH₂), 112.6 (C-5), 157.2 (C-6), 167.7, 171.9. MS: 170 (6, *M*), 169 (0.3), 155 (1), 142 (5), 140 (100), 139 (5), 138 (21), 125 (5), 45 (29). Found: Molecular weight 170.0509. Calc. for C₇H₁₀N₂OS: 170.0514.

4-Hydroxymethyl-2-methylthiopyrimidine (30c). The silyloxymethylpyrimidine (26c, 27c or 28c) 1 mmol) was added to a solution of tetra-*n*-butylammonium fluoride in THF (0.5 M, 4 ml), the resultant solution stirred under nitrogen at ambient temperature overnight, water (50 ml) added, the solution acidified (pH 5) with 1 M acetic acid and the mixture extracted with dichloromethane (3x30 ml). The organic phase was washed with saturated NaCl solution (2x30 ml), dried (MgSO₄), evaporated and the crude product purified by flash chromatography on silica gel using hexane:ethyl acetate 1:1. The structure of the product was verified by comparison with an authentic specimen of the title compound.²³ Yield: 78% from (26c); 62% from (27c); 83% from (28c).

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