Synthesis of a 4-aryl-2-anilinopyrimidine using a germanium-functionalised non cross-linked polystyrene (NCPS) soluble polymeric support

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Supporting Information
General Directions

**Solvents and reagents:** DMF was distilled over CaH₂. MeCN, THF and CH₂Cl₂ were dried and deoxygenated with Grubbs-type solvent purification system. The moisture content of the solvents was monitored by Karl Fischer coulometric titration. Diisopropylamine, triethylamine and trimethyloxysilane were distilled from CaH₂ immediately prior to use. Other reagents and solvents were used as commercially supplied unless otherwise stated.

**Chromatography:** Flash chromatography was performed on silica gel (60 F254, 230-400 mesh) according to the method of W.C. Still. Thin layer chromatography (TLC) was performed on aluminum plates pre-coated with silica (60 F254, 0.2 mm) which were developed using standard visualising agents: ultra violet fluorescence (254 nm), KMnO₄/Δ or vanillin/Δ.

**¹H NMR spectra:** These were recorded at 400 or 250 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak, with the abbreviations s, d, t, and m denoting singlet, doublet, triplet and multiplet respectively.

**¹³C NMR spectra:** These were recorded at 100 or 67 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak.

**Infra red spectra:** These were recorded as thin films or as solids. Only selected absorption frequencies (ν_max) are reported.

**Mass spectra:** Molecular ions and major peaks only are reported for low resolution spectra. Intensities are given as percentages of the base peak. HRMS values are valid to ±5 ppm.

**GPC:** This was performed using a PLgel 5 μM Mixed C column with UV detection at 254 nm and an injection volume of 100 μL and a flow rate of 1 mLmin⁻¹, using toluene as an internal standard.
**Experimental Procedures**

**Trifluoromethanesulfonic acid 4-(2-trimethylgermyl-ethyl)-phenyl ester 5**

Tf$_2$O (106 µL, 0.63 mmol) was added dropwise to a solution of *trimethylgerylphenol* 4$^2$ (100 mg, 0.42 mmol) and DMAP (52 mg, 0.42 mmol) in pyridine (5 mL) at room temperature. After stirring for 5 h at room temperature, the pyridine was removed *in vacuo* and the orange coloured residue was quenched with 0.2M HCl (20 mL) and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic fractions were collected, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by flash chromatography (petrol/EtOAc, 15/1) gave *trimethylgermyl triflate* 5 as a colourless oil (146 mg, 95%). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 0.10 (s, 9H), 0.90-0.95 (m, 2H), 2.55 (m, 2H), 7.04 (d, $J$ = 9Hz, 2H), 7.14 (d, $J$ = 9Hz, 2H) ppm; $^{13}$C NMR (67 MHz, CDCl$_3$): $\delta$ –2.5 (q), 18.4 (t), 30.6 (t), 116.2 (s), 121.0 (d), 121.3 (s), 129.5 (d), 145.6 (s), 147.6 (s) ppm; IR (neat) 2971, 1501, 1426, 1212, 1142, 1018, 889, 823, 757 cm$^{-1}$; MS (EI') m/z 372 (M$^+$'); HRMS calcd. for C$_{12}$H$_{17}$F$_3^{74}$GeO$_3$S 372.0062, found 372.0058 ($\Delta$ = 1.1 ppm).

**Trimethyl-[2-{4-vinyl-phenyl}-ethyl]-germane 6**

To a suspension of *trimethylgermyl triflate* 5 (1.54 g, 4.13 mmol), LiCl (525 mg, 12.4 mmol) and Pd(PPh$_3$)$_4$ (120 mg, 0.025 mmol) in DMF (10 mL) was added tributylvinylstannane (1.34 mL, 4.54 mmol) and the resulting mixture refluxed at 100 °C for 4 h. The DMF was removed *in vacuo* and the resulting residue partitioned between 1M aq. KF (100 mL) and EtOAc (3 × 100 mL). The organic fractions were collected, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by flash chromatography (petrol) gave 4-*trimethylgermylstyrene* 6 as a colourless oil (780 mg, 76%). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 0.15 (s, 9H), 0.92-0.97 (m, 2H), 2.55-2.58 (m, 2H), 5.06 (d, $J$ = 9Hz, 1H), 5.58 (d, $J$ = 18Hz, 1H), 6.57 (dd, $J$ = 18, 9Hz, 1H), 7.04 (d, $J$ = 8.5Hz, 2H), 7.20 (d, $J$ = 8.5Hz, 2H) ppm; $^{13}$C NMR (67 MHz, CDCl$_3$): $\delta$ –2.4 (q), 18.5 (t), 30.9 (t), 112.7 (t), 126.2 (d), 128.0 (d), 135.0 (s), 136.8 (d), 144.9 (s) ppm; IR (neat) 3086, 2907, 1629, 1510, 1407, 990, 909 cm$^{-1}$; MS (EI') m/z 250 (M$^+$'); HRMS calcd. for C$_{13}$H$_{20}^{70}$Ge 250.0777, found 250.0769 ($\Delta$ = 2.0 ppm).
Trimethylgermyl copolymer 8c

A solution of **trimethylgermylstyrene** 6 (135 mg, 0.54 mmol), biphenylstyrene (7c, 408 mg, 2.26 mmol), and DTBP (30 µL, 25 mg) in toluene (8 mL) was freeze-thawed three times with liquid nitrogen and then heated at 110 °C for 18 h. After cooling, the solvent was removed in vacuo and the thick oily residue was dissolved in minimum amount of CH₂Cl₂, precipitated by dropwise addition into cold MeOH (× 3) and collected by centrifugation to give *trimethylgermyl polymer 8c* as white powder (220 mg, 66%, *M.L. 1.63 mmol/g*, as determined by integration of ¹H NMR peaks at δ -0.09 vs. 6.2-7.6 ppm; *m* = 1, *n* = 2.0). PD 2.0, *Mw* 49500, *Mn* 24800; ¹H NMR (250 MHz, CDCl₃): δ -0.09 (br s, 9H), 0.80 (br s, 2H), 1.1-2.2 (m, 6H), 2.48 (br s, 2H), 6.2-7.6 (m, Ar-H, 13H) ppm; IR (CHCl₃) 3026, 2927, 1493, 1452, 1202, 780, 599 (Ge-Me), 453 cm⁻¹.

Chlorodimethylgermyl copolymer 9

Tin(IV) chloride (1.50 mL, 1.45 mmol) was added dropwise to a solution of *trimethylgermyl polymer 8c* (480 mg, ~0.78 mmol) in (nitromethane/o-DCB, 3/1 v/v) at room temperature and the reaction mixture was then heated at 50 °C for 17 h. Volatiles were removed by distillation (85 °C, 0.5 mmHg) to give *chlorodimethylgermyl polymer 9* as a brown paste (495 mg, 91%, *M.L. 1.44 mmol/g*, as determined by integration of ¹H NMR peaks at δ 0.55 vs. 6.2-7.5 ppm; *m* = 1, *n* = 2.4) which was used directly for the subsequent arylation reaction. PD 2.5, *Mw* 46500, *Mn* 18700; ¹H NMR (250 MHz, CDCl₃): δ 0.55 (br s, 6H), 1.1-2.3 (m, 8H), 2.80 (br s, 2H), 6.2-7.5 (m, Ar-H, 13H) ppm; IR (CHCl₃) 3026, 2927, 1493, 1452, 1202, 908, 784, 599 (Ge-Me), 455 cm⁻¹.
Dioxolane germyl copolymer 10

A solution of n-BuLi (1.44 mL, 1.6 M in hexanes, 2.30 mmol) in hexanes was added dropwise to a solution of 4-bromoacetophenone dioxolane (560 mg, 2.30 mmol) in THF (15 mL) at -78 °C. After stirring for 20 min., the reaction mixture was transferred by a cannula to a suspension of chlorodimethylgermyl copolymer 9 (770 mg, ~1.11 mmol) in THF (12 mL) at -78 °C. The resulting mixture was kept at -78 °C for 5 h and then allowed to react at room temperature for 3 h before refluxing at 70 °C for 18 h. The reaction crude was quenched with 1N aq. HCl (30 mL) and extracted with CH$_2$Cl$_2$ (3 × 50 mL). Organic fractions were collected, dried (MgSO$_4$), and concentrated in vacuo. The crude product was re-dissolved in minimum amount of CH$_2$Cl$_2$, precipitated by dropwise addition into cold MeOH (× 3) and collected by centrifugation to give the dioxolane germyl copolymer 10 as white powder (660 mg, 42%, L.L 0.71 mmol/g, as determined by integration of $^1$H NMR peaks at $\delta$ 2.45 & 3.65 vs. 6.0-7.8 ppm; m = 1, n = 5.6). PD 4.5, $M_w$ 62600, $M_n$ 14000; $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 0.20 (br s, 6H), 1.1-2.1 (m, 11H), 2.45 (br s, 2H), 3.65 (br s, 2H), 3.90 (br s, 2H), 6.0-7.8 (m, 17H) ppm; IR (CHCl$_3$) 3010, 2928, 1486, 1039, 837, 746, 603 (Ge-Me), 518 cm$^{-1}$.

Acetophenyl germyl copolymer 11

To a solution of dioxolane germyl copolymer 10 (660 mg, ~0.47 mmol) in THF/H$_2$O (15/2 mL) was added PPTS (15 mg, 0.05 mmol). The mixture was refluxed at 70 °C for 15 h. The solvents were removed in vacuo and the crude re-dissolved in a minimum amount of CH$_2$Cl$_2$, precipitated by dropwise addition into cold MeOH (× 3) and collected by centrifugation to give acetophenyl germyl copolymer 11 as pale yellow white powder (526 mg, 95%, L.L 0.85 mmol/g, as determined
by integration of $^1$H NMR peaks at $\delta$ 0.30 vs. 6.2-8.0 ppm; $m = 1$, $n = 4.5$). $PD$ 3.5, $M_w$ 69100, $M_n$ 19700; $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 0.30 (br s, 6H), 0.9-2.4 (m, 10H), 2.60 (br s, 3H), 6.2-8.0 (m, 17H) ppm; IR (CHCl$_3$) 3010, 2928, 1681 (C=O), 1486, 793, 603 (Ge-Me), 458 cm$^{-1}$.

**Enaminone germyl copolymer 12**

![Diagram](image)

To a suspension of *acetophenyl germyl copolymer* 11 (520 mg, ~0.44 mmol) in THF (15 mL) at RT was added Bredereck’s reagent (1.07 mL, 5.2 mmol). The resulting mixture was refluxed at 70 °C for 18 h. The solvents were removed *in vacuo* and the crude was dissolved in minimum amount of CH$_2$Cl$_2$, precipitated by dropwise addition into cold MeOH ($\times$ 3) and collected by centrifugation to give *enaminone germyl copolymer* 12 as yellow white powder (450 mg, 81%, *L.L. 0.79 mmol/g*, as determined by integration of $^1$H NMR peaks at $\delta$ 0.05 vs. 6.1-7.9 ppm; $m = 1$, $n = 4.7$); $PD$ 3.7, $M_w$ 23200, $M_n$ 6200; $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 0.05 (br s, 6H), 0.7-2.0 (m, 8H), 2.30 (br s, 2H), 2.2-3.0 (m, 6H), 5.47 (br d, $J = 8$Hz, 2H), 6.1-7.9 (m, 18H) ppm; IR (CHCl$_3$) 3013, 2928, 1642 (C=O), 1566 (C=C), 1486, 1265, 784, 603 (Ge-Me), 470 cm$^{-1}$.

**4-Guanidinobenzoic acid methyl ester hydrochloride 13**

![Diagram](image)

SOCl$_2$ (600 µL, 8.2 mmol) was added to MeOH (5 mL) over 10 minutes at −10 °C followed by the addition *4-guanidino-benzoic acid hydrochloride* (300 mg, 1.39 mmol). The reaction mixture was then allowed to stir at room temperature for 90 min before heating to 45 °C for 8 h. The resulting solution was evaporated to dryness under vacuum and MeOH was added twice and evaporated. The resulting white solid was recrystallised (MeOH/Et$_2$O) to give *4-guanidinobenzoic acid methyl ester hydrochloride* 13 as white needles (140mg, 44%); mp 252-253 °C; $^1$H NMR (250 MHz, $d_6$-DMSO): $\delta$ 3.85 (s, 3H), 7.34 (d, $J=7.5$Hz, 2H), 7.80 (br s, 3H), 7.98 (d, $J=7.5$Hz, 2H), 10.50 (br s, 1H) ppm; $^{13}$C NMR (67 MHz, $d_6$-DMSO): $\delta$ 52.6 (q), 123.0 (d), 126.6 (s), 131.1 (d), 140.8 (s), 156.0 (s), 166.0 (s) ppm; IR (neat) 3318, 3144, 1679, 1576, 1288, 1116, 769 cm$^{-1}$; MS (EI$^+$) $m/z$ 193 (M$^+$), 151, 120, 92; HRMS (ES$^+$) calcd. for C$_9$H$_{12}$N$_2$O$_2$ 193.0930, found 194.0934 ($\Delta = 2.1$ ppm).
Pyrimidine germyl copolymer 14 and 2-anilino-4-arylpyrimidine 3

To a solution of enaminone germyl copolymer 12 (150 mg, ~0.12 mmol) and K₂CO₃ (104 mg, 0.75 mmol) in DMF (10 mL) was added 4-guanidinobenzoic acid methyl ester hydrochloride 13 (69 mg, 0.30 mmol). The resulting mixture was heated at 120 °C for 24 h. The solvent was removed in vacuo and the crude residue was dissolved in a minimum amount of CH₂Cl₂ and filtered through a short pad of Celite®. The filtrate was precipitated by dropwise addition into cold MeOH (× 3) and collected by centrifugation. The resulting sticky pale yellow solid, copolymer 14 (150 mg) was dissolved in THF (15 mL) and recrystallized N-chlorosuccinimide (60 mg, 0.45 mmol) added. The resulting solution was heated at 70 °C for 8 h. The solvent was removed in vacuo and the crude material was dissolved in minimum amount of CH₂Cl₂, the unwanted polymer precipitated by dropwise addition into cold MeOH and filtered-off using a short pad of Celite®. The filtrate was concentrated in vacuo and the resulting pale yellow solid was purified by flash chromatography (petrol/EtOAc, 7/3) to give 2-anilino-4-arylpyrimidine 3 as white solid (30 mg, 74%). mp 228-229 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.60 (bs, 1H), 3.85 (s, 3H), 7.14 (d, J= 5Hz, 1H), 7.43 (d, J= 7Hz, 2H), 7.73 (d, J= 7Hz, 2H), 7.98 (app t, J= 7Hz, 4H), 8.44 (d, J= 5Hz, 1H) ppm; ¹³C NMR (100 MHz, d₆-DMSO): δ 51.8, 109.0, 117.8, 121.8, 128.8, 129.1, 130.3, 135.2, 145.2, 159.4, 159.7, 162.6, 166.0 ppm; IR (neat) 3320, 1700, 1532, 1434, 1316, 1177 cm⁻¹; MS (ES⁺) m/z 342/340 ([35Cl/37Cl, MH⁺]), HRMS calcd. for C₁₈H₁₅ClN₄O₂ 340.0853, found 340.0870 (Δ = 5.0 ppm).

Phenyl-[4-(4-trimethylgermanyl-phenyl)-pyrimidin-2-yl]-amine 16

To a solution of enaminone 15 (50 mg, 0.171 mmol) and phenylguanidine (128 mg, 0.510 mmol) in CH₂Cl₂ (10 mL) was added NaOMe (46 mg, 0.85 mmol). The resulting mixture was refluxed at 50 °C for 18 h. It was then partitioned between 0.2 M NaOH (30 mL) and CH₂Cl₂ (3 × 30 mL). Purification by flash chromatography (DCM/MeOH, 9/1) gave 2-anilinopyrimidine 16 as a pale yellow solid (50 mg,
81%); mp 160-162 °C (petrol); $^1$H NMR (CDCl$_3$): $\delta$ 0.35 (s, 9H), 7.00 (t, $J$ = 8Hz, 1H), 7.08 (d, $J$ = 5Hz, 1H), 7.24-7.34 (m, 3H), 7.55 (d, $J$ = 8Hz, 2H), 7.64 (d, $J$ = 8Hz, 2H), 7.96 (d, $J$ = 8Hz, 2H), 8.40 (d, $J$ = 5Hz, 1H) ppm; $^{13}$C NMR (CDCl$_3$): -1.8 (q), 108.4 (d), 119.2 (d), 122.4 (d), 126.4 (d), 128.9 (d), 133.5 (d), 135.5 (s), 139.7 (s), 145.8 (s), 158.5 (d), 160.3 (s), 165.1 (s) ppm; IR (CHCl$_3$) 3028, 1576, 1439, 1207, 804, 763, 603 (Ge-Me) cm$^{-1}$; MS (EI$^+$) m/z 365 (M$^+$); HRMS calcd. for C$_{19}$H$_{21}$GeN$_3$ 365.0947, found 365.0939 (Δ = 2.1 ppm).
NMR Spectra and GPC Chromatograms

$^1$H NMR 250 MHz, CDCl$_3$
$^{13}$C NMR 67 MHz, CDCl$_3$
$^1$H NMR 250 MHz, CDCl$_3$
$^{13}$C NMR 67 MHz, CDCl$_3$
GPC

Polymer Laboratories
PL.iLogiCal GPC Software

Unknown: 11046.004
Acquired: Operator

Concentration: Detector: UV@254nm
Injection Volume: Temperature: 40°C
Solvent: Chloroform
Column Set: Flow Rate: 1.000
2 x PL Gel S micron mixed bed C end guard Standards: Polyethylene

Method:
Comments: Flow marker = toluene

Calibration Using:
Nemix Standards
Calibration Limits: 9.80 to 17.42 Mins
Flow Rate Marker: found at: 10.80 Mins
Last Calibrated: Tue Mar 27 10:44:40 2001
in Standards at: 19:48 Mins

Broad Peak Start: 11:43 End: 16:02 Mins

Molecular Weight Averages
Mw = 40025 Mz = 61302
Mn = 18065 Mz+1 = 125162
Mw/Mn = 46462 Mv = 43193
Polydispersity = 2.486 Peak Area = 1875532
'H NMR 250 MHz, CDCl₃
Polymeric Laboratories
PL. LogiCal GPC Software

Unknown: 12041.032
Acquired: Operator

Concentration: 
Detector: UV@254nm

Injection Volume: 
Temperature: 40C

Solvent: Chloroform
Flow Rate: 1.000

Column Gel: 2 x PL Gel 5 micron mixed bed C and guard
Standards: Polystyrene

Method: 1
Comments: Flow manner = toluene

Calibration Using: Narrow Standards
Curve Used: 5th Order Polynomial

Calibration Limits: 9.83 to 17.47 Mins
Last Calibrated: Tue Mar 27 10:44:40 2001

Flow Rate Marker: Found at: 19.87 Mins
In Standards at: 19.88 Mins

Molecular Weight Averages

Mn = 13,563
Mw = 63,994
Mz = 17,744

Polydispersity = 4.483
Peak Area = 62,676
$^1$H NMR 250 MHz, CDCl$_3$
Polymet Laboratories
PL Logical GPC Software

Unknown 11041.000

Concentration: 
Injection Volume: 
Solvent: Chloroform
Column Set: 2 x PL Gel 5 micron mixed bed C and guard
Method: 1
Comments: Flow marker = toluene

Calibration Using: Narrow standards
Calibration Limits: 9.82 to 17.43 Minutes
Flow Rate Marker: found at: 19.83 in standards at: 19.88 Minutes

Acquired: Operator
Detector: UVI@254nm
Temperature: 40°C
Flow Rate: 1.000
Standards: Polystyrene

Molecular Weight Averages
Mw = 49629  Mz = 209723
Mn = 19688  Mz+1 = 806410
Mn+1 = 59140  Mv = 50130
Polydispersity = 3.512  Peak Area = 2223379
$^1$H NMR 250 MHz, CDCl$_3$
$^1$H NMR 250 MHz, $d_6$-DMSO
$^1$H NMR 67 MHz, $d_6$-DMSO
$^1$H NMR 400 MHz, CDCl$_3$
$^{13}\text{C NMR 100 MHz, } d_6\text{-DMSO}$
$^{1}\text{H NMR 250 MHz, CDCl}_{3}$
$^{13}$C NMR 67 MHz, CDCl$_3$
References


