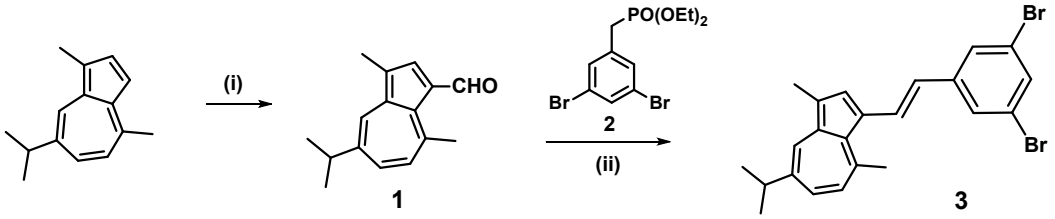
Electronic supplementary information

Synthesis of the 1,3-dibromophenyl derivative intermediates

PATHWAY A



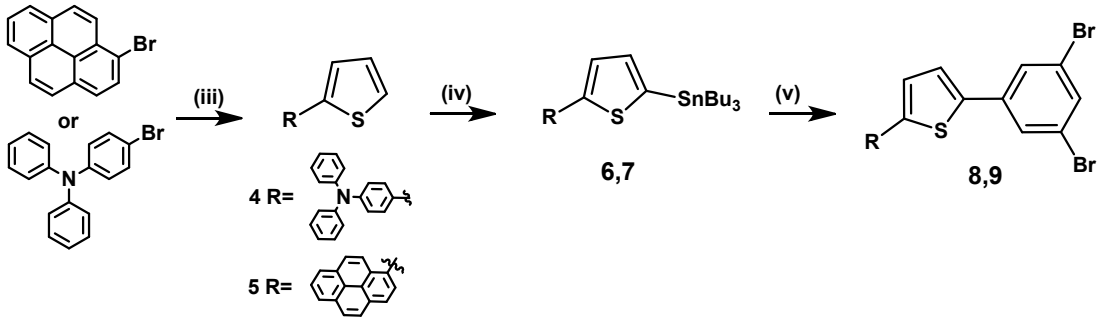
Reagents and conditions: (i) $POCl_3$, 1,2dichloroethane, DMF, rt then 80°C, 20 min; (ii) *t*-BuOK, THF, Ar, 0°C, then rt, 15 h.

1-guaiazulenecarboxaldehyde (1). Guaiazulene (500 mg, 3.16 mmol) and DMF (5 mL) were degassed in a two-necked-round-bottomed flask, then a mixture of phosphoryl chloride (324 µL, 3.47 mmol), 1,2-dichloroethane (3.6 mmol) in DMF (1 mL) was slowly added. A brownish solid formed. After stirring for 5 minutes at room temperature, the mixture was heated at 80°C for 20 minutes, until the solid dissolved. NaOH 1.25 M (20 mL) was added to break the aggregate. Purification: The mixture was extracted into CH_2Cl_2, the organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (silica, hexane:Et_2O, 6:4 to 1:1). The desired product was obtained as a blue oil (430 mg). Yield: 60% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.65 (1H, s), 8.31 (1H, d, *J* = 2 Hz), 8.24 (1H, s), 7.60 (1H, dd, *J* = 2 Hz, 10.8 Hz), 7.43 (1H, d, *J* = 10.8 Hz), 3.19 (1H, d, *J* = 6.9 Hz), 3.17 (3H, s), 2.60 (3H, s), 1.41 (6H, d, *J* = 6.9 Hz).

2. Diethyl 3,5-dibromobenzylphosphonate was prepared starting from the 3,5-dibromobenzaldehyde according to the literature.[1]

3. Guaiazulene-1-carboxaldehyde (453 mg, 1.17 mmol) and diethyl 3,5-dibromobenzylphosphonate (**2**, 240 mg, 1.07 mmol) were dissolved in THF (10 mL) under Ar atmosphere at 0°C. *t*-BuOK (315 mg, 2.78 mmol) was added in small portions to the solution over 20 minutes, keeping the mixture under stirring. The mixture was then allowed to warm gradually at room temperature and stirred overnight. Afterwards, H_2O was added causing the formation of a precipitate and the mixture was stirred for 30 minutes. The solvent was partially removed under reduced pressure, the residue was extracted into CH_2Cl_2, the organic layer was dried over $MgSO_4$ and removed under reduced pressure. The crude product was purified by column chromatography (silica, hexane:CH_2Cl_2, 6:4). The desired product was obtained as a bluish green laque (115 mg). Yield: 23%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07 (1H, d, *J* = 1.7 Hz), 8.01 (1H, d, *J* = 15.7 Hz), 7.88 (1H, s), 7.53 (1H, s), 7.50 (1H, d, *J* = 11.4 Hz), 7.30 (2H, m), 6.93 (1H, d, *J* = 10.6 Hz), 6.69 (1H, d, *J* = 15.7 Hz), 3.05 (4H, m), 2.65 (3H, m), 1.39 (6H, d, *J* = 6.9 Hz).

PATHWAY B



Reagents and conditions: (iii) 2-(tri-*n*-butylstannyl)thiophene, $Pd(PPh_3)_4$, toluene, 110°C, 24 h; (iv) *n*-BuLi, Bu_3SnCl, THF, Ar, -50°C to rt, 15 h; (v) 1,3,5-tribromobenzene, $Pd(PPh_3)_4$, toluene, 110°C, 48h.

4. A mixture of 4-bromo-N,N-diphenylaniline (750 mg, 2.3 mmol), 2-(tri-*n*-butylstannyl)thiophene (1.10 mL, 3.4 mmol) and $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) was suspended in toluene (40 mL) and heated at reflux under argon atmosphere for 24 h. After cooling to room temperature, an aqueous solution of NaOH 1 M was added. The resulting solution was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, hexane:CH_2Cl_2, 9:1). The desired product was obtained as a pale yellow solid (753 mg). Yield: quantitative. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.53 (2H, d, *J* = 6.7 Hz), 7.30 (6H, m), 7.13 (2H, d, *J* = 7.6 Hz), 7.08 (7H, m).

5. A mixture of 1-bromopyrene (200 mg, 0.71 mmol), 2-(tri-*n*-butylstannyl)thiophene (339 µL, 1.07 mmol) and $Pd(PPh_3)_4$ (41 mg, 0.035 mmol) was suspended in toluene(10 mL) and heated at reflux under argon atmosphere for 24 h. After cooling to room temperature, an aqueous solution of NaOH 1 M was added. The resulting solution was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, hexane:CH_2Cl_2, 1:9 to 7:3). The desired product was obtained as a yellow laque (176 mg). Yield: quantitative. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.60 (1H, d, *J* = 9.2 Hz), 8.20 (4H, m), 8.08 (4H, m), 7.61(1H, d, *J* = 5.1 Hz), 7.48 (1H, d, *J* = 3.4 Hz), 7.28 (1H, t, *J* = 5.1 Hz).

6. A solution of **4** (753 mg, 2.3 mmol) in THF (50 mL) was placed in a dried two-necked-round-bottomed flask under argon atmosphere. The mixture was cooled to -50°C and degassed, *n*-BuLi 1.6M (1.6 mL, 2.73 mmol) was added, then the mixture was allowed to warm gradually at -10°C and stirred for 30 minutes. The mixture was cooled to -40°C, Bu_3SnCl (736 µL, 2.73 mmol) was added, then the mixture was allowed to warm gradually at room temperature and stirred overnight. H_2O was added to quench the reaction, the mixture was stirred for 15 minutes and extracted into Et_2O. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. ^{1}H-NMR was used to assess the purity of the stannane. The product was obtained as a brown oil (1.42 g). Yield: quantitative. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71 (1H, m), 7.53 (1H, m), 7.48 (1H, d, *J* = 8.5 Hz), 7.26 (5H, m), 7.12 (3H, d, *J* = 7.8 Hz), 7.02 (5H, m), 1.76-0.93 (36H, m).

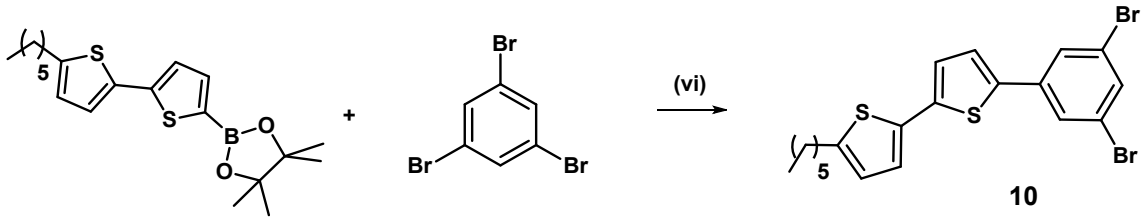
7. A solution of **5** (176 mg, 0.71 mmol) in THF (14 mL) was placed in a dried two-necked-round-bottomed flask under argon atmosphere. The mixture was cooled to -50°C and degassed, *n*-BuLi 1.6M (530 µL, 0.85 mmol) was added, then the mixture was allowed to warm gradually at -10°C and stirred for 30 minutes. The mixture was cooled to -40°C, Bu_3SnCl (229 µL, 0.85 mmol) was added, then the mixture was allowed to warm gradually at room temperature and stirred overnight. H_2O was added to quench the reaction, the mixture was stirred for 15 minutes and extracted into Et_2O. The organic layer was dried over $MgSO_4$,

filtered and the solvent was removed under reduced pressure. ^{1}H-NMR was used to assess the purity of the stannane. The desired product was obtained as a brownish oil (407 mg). Yield: quantitative. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.69 (1H, d, *J* = 9.3 Hz), 8.23 (1H, d, *J* = 7.9 Hz), 8.17 (3H, d, *J* = 7.8 Hz), 8.10 (1H, d, *J* = 9.3Hz), 8.05 (2H, s), 8.01(1H, t, *J* = 7.6 Hz), 7.64 (1H, d, *J* = 3.1 Hz), 7.47 (1H, d, *J* = 3.1 Hz), 1.84 (6H, m), 1.58 (6H, m), 1.36 (6H, m), 1.12 (9H, m).

8. A mixture of **6** (277 mg, 0.45 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol) and 1,3,5-tribromobenzene (130 mg, 0.41 mmol) was suspended in toluene (0.5 mL) and heated at reflux under argon atmosphere for 48 h. After cooling to room temperature, an aqueous solution of NaOH 1 M was added. The resulting solution was extracted with AcOEt and the organic layer was dried over $MgSO_4$ and removed under reduced pressure. The crude product was purified by flash chromatography (silica, hexane: CH_2Cl_2, 9:1 to 8:2). The desired product was obtained as a yellow solid (167 mg). Yield: 67%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69 (2H, d, *J* = 1.5), 7.56 (1H, s, *J* = 1.5 Hz), 7.49 (2H, d, *J* = 8.6 Hz), 7.32 (2H, d, *J* = 8.3 Hz), 7.28 (2H, m), 7.21 (1H, d, *J* = 3.8 Hz), 7.16 (4H, d, *J* = 7.6 Hz), 7.09 (5H, m).

9. A mixture of **7** (407 mg, 0.71 mmol), 1,3,5-tribromobenzene (302 mg, 0.47 mmol) and $Pd(PPh_3)_4$ (28 mg, 0.024 mmol) was suspended in toluene (10 mL) and heated at reflux under argon atmosphere for 48 h. After cooling to room temperature, an aqueous solution of NaOH 1 M was added. The resulting solution was extracted with AcOEt and the organic layer was dried over $MgSO_4$ and removed under reduced pressure. The crude product was purified by flash chromatography (silica, hexane:CH_2Cl_2, 1:9). The desired product was obtained as a yellow laque (74 mg). Yield: 20%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.57 (1H, m), 8.23 (3H, m), 8.13 (5H, m), 8.06 (1H, t, *J* = 7.5 Hz), 7.80 (1H, d, *J* = 1.3Hz), 7.63 (1H, d, *J* = 4.0 Hz), 7.48 (1H, d, *J* = 3.6 Hz), 7.38 (1H, d, *J* = 3.5 Hz).

PATHWAY C

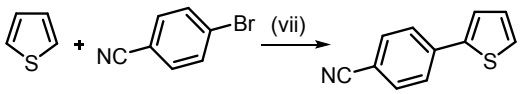


Reagents and conditions: (vi) $Pd(PPh_3)_4$, Na_2CO_3, THF/H_2O, 90°C, 24 h.

10. A suspension of 1,3,5-tribromobenzene (150 mg, 0.47 mmol), 5'-Hexyl-2,2'-bithiophene-5-boronic acid pinacol ester (175 mg, 0.47 mmol), $Pd(PPh_3)_4$ (81 mg, 0.07 mmol) and Na_2CO_3 (7.5 mg, 0.07 mmol) in a mixture of THF/H_2O 1:1 (16 mL) was heated at 90°C for 24 hours. The mixture was then allowed to cool to room temperature, extracted in CH_2Cl_2/H_2O. The organic phase was dried over Na_2SO_4, the solvent removed under reduced pressure, and the crude was purified by flash chromatography (silica, hexane:CH_2Cl_2, 1:1). The desired product was obtained as a yellowish oil (150 mg). Yield: 66%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (1H, s), 7.50 (2H, d, *J* = 4.5 Hz) 7.48 (2H, bs), 7.45 (2H, s) 6.83 (1H, d, *J* = 4.5 Hz), 2.84 (2H, m), 2.11 (2H, m), 1.57 (6H, m), 0.88 (3H, t).

Synthesis of 4-(thiophen-2-yl)benzonitrile, intermediate of ligand L5

PATHWAY D



11

Reagents and conditions: (vii) $Pd(OAc)_2$, KOAc, DMA, 150°C, 16h.

11.[2] To a 50 mL oven dried Schlenk tube, thiophene (1.28 mL, 16 mmol), 4-bromobenzonitrile (728 mg, 4 mmol), KOAc (784 mg, 8 mmol), $Pd(OAc)_2$ (18 mg, 0.08 mmol) and DMA (16 mL) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 16 hours. After cooling the reaction at room temperature and concentration, the crude was purified by flash chromatography on silica gel (pentane-EtOAc, 85-15) to afford the desired compound (608 mg, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (d, 2H, *J* = 7.1 Hz), 7.63 (d, 2H, *J* = 7.1 Hz), 7.43-7.37 (m, 2H), 7.12 (m, 1H).

References

1. E. Diez-Barra, J. C. Garcìa-Martìnez, S. Merino, R. del Rey, J. Rodrìguez-Lòpez, P. Sànchez-Verdù and J. Tejeda, J. Org. Chem., 2001, **66**, 5664.

2. G.A. Molander, B. Canturk, L.E. Kennedy, *J. Org. Chem.,* 2009, **74**, 973.