Preparation of Maruoka’s catalyst 13

The catalyst **13** described by the Maruoka group was prepared as follow (Scheme 1). [[1](#_ENREF_1),[2](#_ENREF_2)] Trimethoxybenzoic acid **41** was brominated in CH3CN with NBS (step i) followed by conversion of the carboxylic acid **42** to the methyl ester **43** with TMS-Cl in MeOH (step ii).[[2](#_ENREF_2),[3](#_ENREF_3)] The Ullmann biaryl coupling of **43** to form bicyclic **44** was performed in NMP with activated copper bronze by adapting a general procedure (step iii).[[4](#_ENREF_4),[5](#_ENREF_5)] Saponification and precipitation by acidification yielded diacid **45**, in multigram quantity, which was purified by recrystallization (step iv). The diacid **45** was treated with two equivalents of quinidine forming the double salt **46** (step v). Resolution of **46** by three fractional crystallizations was done by following the litterature procedure (step vi).[[6](#_ENREF_6)] In this case, after resolution, the acid (*R*)-**45** was obtained with high enantiopurity (≥ 99%, step vii). Treatment of (*R*)-**45** with TMS-Cl in MeOH for 72 h, at rt, gave the diester (*R*)-**44** (step viii).[[3](#_ENREF_3)] From this product the catalyst was made by following the Maruoka’s patented method (steps ix-xiii).[[2](#_ENREF_2)] After purification by preparative HPLC, the overall yield of (*R*)-**13** from (*R*)-**45** was 30% (steps viii-xiii). In the same way (*S*)-**13** was also obtained from(*S*)-**45**.



**Scheme 1**. Synthesis of Maruoka's catalyst. i) NBS, CH3CN, 2 °C, 16 h, 93%; ii) TMS-Cl, MeOH, rt, 48 h, 94%; iii) Cu, NMP, 170 °C, 2 h; iv) NaOH, aq. MeOH, reflux, 16 h, then aq. HCl, 0 °C, 77%; v) quinidine (2 eq), aq. EtOH; vi) fractional crystallizations (3 x); vii) NaOH, HCl; viii) TMS-Cl, MeOH, rt, 48 h, 96%; ix) Br2, CH3CN, rt, 16 h, 80%; x) 3,4,5-F3-PhB(OH)2 (3 eq.), Pd(OAc)2 (20 mol%), tri-*o*-tolyl-P (80 mol%), NaOMe (3 eq.), DME, 80 °C, 16 h, 75% ; xi) LiAlH4, rt, 4 h, 85%; xii) PBr3 (3 eq.), CH2Cl2, 0 °C, 2 h, 91%; Bu2NH (1.3 eq), K2CO3, CH3CN, 85 °C, 16 h, 67%.

2-Bromo-3,4,5-trimethoxybenzoic acid 42

The procedure described in Maruoka’s patent was modified as follows by using CH3CN in place of CHCl3.[[2](#_ENREF_2)] Small portions of NBS (89 g, 500 mmol) was added during 10 min to an ice-cold solution of 3,4,5-trimethoxybenzoic acid **41** (106 g, 500 mmol) in CH3CN (1 L). The resulting mixture was stirred for 16 h at 2 °C. The solvent was evaporated *in vacuo* and the resulting solids were dissolved in boiling water (1 L) containing NaOH (22 g, 550 mmol). The solution was cooled to 10 °C and acidified with an excess of HCl (pH: 3). The precipitate was filtered, washed with water and dried *in vacuo* to constant weight. The *title compound* (135.5 g, 93%) was obtained as a beige solid. Mp 145-148 °C; 1H NMR (250 MHz, CDCl3) δH 12.29 (s, 1H, OH), 7.38 (s, 1H, Ar-H), 3.94 (s, 3H, OCH3), 3.88 (s, 3H, OCH3), 3.87 (s, 3H, OCH3); 13C NMR (63 MHz, CDCl3) δC 171.20 (CO), 152.19 (Ar-C), 151.68 (Ar-C), 147.05 (Ar-C), 125.37 (Ar-C), 111.31 (Ar-C), 110.97 (Ar-C), 61.24 (OCH3), 61.07 (OCH3), 56.29 (OCH3); *m/z* (ESI) 289/291 [M]-.

Methyl 2-bromo-3,4,5-trimethoxybenzoate 43

To compound **42** (135.5 g, 466 mmol) in MeOH (500 mL) was added TMS-Cl (250 mL, 1.97 mol).[[3](#_ENREF_3)] The solution was stirred for 48 h at rt. The solvents were evaporated and the residue was dissolved in CH2Cl2. The organic layer was washed with water, aqueous saturated NaHCO3 and water. The organics were dried on MgSO4, filtered and the solvent evaporated *in vacuo* to give the *title compound* (134 g, 94%) as a golden oil. 1H NMR (250 MHz, D2O) δH 7.10 (s, 1H, Ar-H), 3.87 (s, 3H, OCH3), 3.86 (s, 3H, OCH3), 3.83 (s, 6H, OCH3); 13C NMR (63 MHz, CDCl3) δC 166.37 (CO), 152.30 (Ar-C), 151.47 (Ar-C), 145.98 (Ar-C), 127.41 (Ar-C), 110.06 (Ar-C), 109.43 (Ar-C), 61.11 (OCH3), 60.97 (OCH3), 56.21 (OCH3), 52.45 (OCH3); *m/z* (ESI) 305/307 [MH]+.

4,4',5,5',6,6'-Hexamethoxybiphenyl-2,2'-dicarboxylic acid 45

In order to conduct the reaction at lower temperature and to increase yield, the synthesis was done by modifying the known literature method and a solvent, NMP, was added. [[4](#_ENREF_4),[5](#_ENREF_5)] Compound **43** (133 g, 436 mmol) was dissolved in NMP (150 mL) and the solution was heated to 170 °C under nitrogen. Activated copper bronze (115 g, [iodine (2%) in acetone, aqueous HCl (10 M)/acetone:1/1][[7](#_ENREF_7)]) was added in one portion and the suspension was stirred for 2 h. The dark brown mixture was cooled to 100 °C and the copper was filtered on celite and washed with boiling toluene. After solvents evaporation *in vacuo* (0.1 mm Hg) at 95 °C, a dark brown oil contaminated by solids was obtained. The crude product **44** was dissolved in EtOAc and washed twice with ammonium hydroxide (6 M) and water. After evaporation, a brown oil was obtained (100 g). The crude diester **44** was saponified by heating under reflux for 16 h with a solution of NaOH (50 g) in MeOH/H2O (1/1; 400 mL). The MeOH was evaporated *in vacuo*.The volume of the solution was adjusted to 500 mL with H2O and hydrochloric acid was added under stirring until pH 3. The suspension was cooled to 0 °C, the precipitate **45** was filtered and washed with water. The wet solid was recrystallized twice from boiling aqueous MeOH. After filtration and drying to constant weight the *title compound* (71 g, 77 %) was obtained as an off-white solid. Mp 248-249 °C; 1H NMR (250 MHz, DMSO) δH 12.24 (s, 2H, COOH), 7.32 (s, 2H, Ar-H), 3.87 (s, 6H, OCH3), 3.81 (s, 6H, OCH3), 3.49 (s, 6H, OCH3); 13C NMR (63 MHz, DMSO) δC 167.29 (CO), 151.44 (Ar-C), 150.81 (Ar-C), 144.49 (Ar-C), 126.61 (Ar-C), 125.80 (Ar-C), 108.94 (Ar-C), 60.37 (OCH3), 60.11 (OCH3), 55.74 (OCH3); *m/z* (ESI) 421 [M]-.

**(*R*)-4,4',5,5',6,6'-Hexamethoxybiphenyl-2,2'-dicarboxylic acid (*R*)-45**

Resolution of compound **45** was realized through the diquinidinium salt **46** by following the known method. [[6](#_ENREF_6)] Ee was determined on a Chiracel OD-H column (Daicel, 150 mm × 4 mm, 5 µm); mobile phase: *n*-Hex/*i*-PrOH/TFA:90/10/0.1; 0.8 mL/min; 37 °C. Retention times for isomers *R* and *S* were 8.3 min and 11.0 min, respectively. Enantiomeric purity of (*R*)-**45** was ≥ 99%. Enantiomer (*S*)-**45** was also obtained with an ee ≥ 99%.

Dimethyl (*R*)-4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-dicarboxylate (*R*)-44

A mixture of (*R*)-**45** (7.4 g, 17.5 mmol) and TMS-Cl (19 mL, 150 mmol) in MeOH (200 mL) was stirred for 72 h at rt. The solvents were evaporated and the residue was dissolved in CH2Cl2. The organic layer was washed with water, aqueous saturated NaHCO3 and water. The organics were dried on MgSO4, filtered and the solvent evaporated *in vacuo* to give the *title compound* (7.8 g, 95%) as a golden oil. 1H NMR (250 MHz, CDCl3) δH 7.34 (s, 2H, Ar-H), 3.91 (s, 6H, OCH3), 3.90 (s, 6H, OCH3), 3.57 (s, 12H, OCH3); 13C NMR (63 MHz, CDCl3) δC 166.89 (CO), 152.04 (Ar-C), 151.23 (Ar-C), 145.40 (Ar-C), 126.58 (Ar-C), 124.96 (Ar-C), 108.86 (Ar-C), 60.77 (OCH3), 60.51 (OCH3), 55.93 (OCH3), 51.80 (OCH3); *m/z* (ESI) 451 [MH]+.

Dimethyl (*R*)-3,3'-dibromo-4,4',5,5',6,6'-hexamethoxy biphenyl-2,2'-dicarboxylate (*R*)-47

The *title compound* was obtained as colourless needles as previously described.[[2](#_ENREF_2)] Mp 114-115 °C; 1H NMR (250 MHz, CDCl3) δH 3.92 (s, 6H, OCH3), 3.91 (s, 6H, OCH3), 3.76 (s, 6H, OCH3), 3.61 (s, 6H, OCH3); 13C NMR (63 MHz, CDCl3) δC 166.23 (CO), 151.83 (Ar-C), 151.49 (Ar-C), 148.00 (Ar-C), 130.90 (Ar-C), 125.06 (Ar-C), 109.53 (Ar-C), 61.16 (OCH3), 61.03 (OCH3), 60.94 (OCH3), 52.08 (OCH3); *m/z* (ESI) 607 (1)/609 (2)/611 (1) [MH]+.

Dimethyl (R)-3,3'-bis(3,4,5-trifluorophenyl)-4,4',5,5',6,6'-hexa methoxybiphenyl-2,2'-dicarboxylate (*R*)-48

The *title compound* was obtained as an amber oil as previously described.[[2](#_ENREF_2)] 1H NMR (250 MHz, CDCl3) δH 7.03 – 6.83 (m, 4H, Ar-H), 4.00 (s, 6H, OCH3), 3.88 (s, 6H, OCH3), 3.72 (s, 6H, OCH3), 3.29 (s, 6H, OCH3); 13C NMR (63 MHz, CDCl3) δC 167.11 (CO), 152.31 (Ar-C), 151.01 (Ar-C), 150.54 (Ar-C) (ddd, *JC-F* = 249.4, 9.8, 4.1 Hz, Ar-C), 147.62 (Ar-C), 139.00 (dt, *JC-F* = 251.8, 15.2 Hz, Ar-C), 132.37 (td, *JC-F*= 8.1, 4.8 Hz, Ar-C), 128.91 (Ar-C), 127.08 (Ar-C), 125.24 (Ar-C), 114.30 – 113.91 (m, Ar-C), 113.82 (Ar-C), 61.11 (OCH3), 60.81 (OCH3), 51.55 (OCH3); *m/z* (ESI) 711 [MH]+.

(*R*)-3,3'-bis(3,4,5-trifluorophenyl)-4,4',5,5',6,6'-hexamethoxy biphenyl-2,2'-dimethanol (*R*)-49

The *title compound* was obtained as a beige powder as previously described.[[2](#_ENREF_2)] Mp ; 1H NMR (250 MHz, CDCl3) δH 7.18 – 7.00 (m, 4H, Ar-H), 4.02 (d, *J* = 11.3 Hz, 2H, CH2), 3.94 (s, 6H, OCH3), 3.93 (d, *J* = 11.1 Hz, 2H, CH2), 3.75 (s, 6H, OCH3), 3.70 (s, 6H, OCH3), 3.01 (b, 2H, OH); 13C NMR (63 MHz, CDCl3) δC 151.40 (Ar-C), 151.06 (Ar-C), 150.56 (ddd, *JC-F* = 249.5, 9.8, 4.2 Hz, Ar-C), 146.05 (Ar-C), 139.18 (dt, *JC-F* = 251.5, 15.3 Hz, Ar-C), 133.49 (Ar-C), 132.20 (td, *JC-F* = 8.3, 5.2 Hz, Ar-C), 130.48 (Ar-C), 126.51 (Ar-C), 114.95 (b, Ar-C), 61.13 (OCH3), 60.88 (OCH3), 60.80 (OCH3), 59.65 (CH2); *m/z* (ESI) 655 [MH]+.

(*R*)-3,3'-bis(3,4,5-trifluorophenyl)-4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-dimethyl bromide (*R*)-50

The title compound was obtained as a white solid as previously described[[2](#_ENREF_2)] and was used without purification for the next step; *m/z* (ESI) 779 (1)/781 (2)/783 (1) [MH]+.

Chiral quaternary ammonium salt (*R*)-13

The title compound was obtained as a white solid as previously described.[[2](#_ENREF_2)] Mp ; 1H NMR (250 MHz, CDCl3) δH 7.39 – 7.09 (m, 4H, Ar-H), 4.45 (d, *J* = 13.7 Hz, 2H, CH2Ar), 4.08 (s, 6H, OCH3), 3.94 (s, 6H, OCH3), 3.84 (d, *J* = 14.1 Hz, 2H, CH2Ar), 3.78 (s, 6H, OCH3), 3.06 (t, *J* = 12.5 Hz, 2H, NCH2), 2.80 (b, 2H, NCH2), 1.26 – 0.96 (m, 6H, CH2), 0.80 (t, *J* = 5.7 Hz, 6H, CH3), 0.24 (b, 2H, CH2); 13C NMR (63 MHz, CDCl3) δC 152.40 (Ar-C), 152.00 (Ar-C), 151.00 (dtd, *JC-F* = 252.1, 9.2, 3.7 Hz, Ar-C), 148.11 (Ar-C), 139.54 (dt, *JC-F* = 253.9, 15.0 Hz, Ar-C), 130.47 (td, *J* = 8.0, 5.3 Hz, Ar-C), 130.05 (Ar-C), 126.80 (Ar-C), 120.29 (Ar-C), 115.75 (dd, *JC-F* = 17.9, 2.3 Hz, Ar-C), 61.63 (OCH3), 61.18 (OCH3), 61.01 (OCH3), 57.76 (CH2Ar), 57.17 (NCH2), 24.32 (CH2), 19.34 (CH2), 13.24 (CH3); *m/z* (ESI) 748 [M]+.

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