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One-Pot Synthetic Procedure for 2,2′-Disubstituted Biaryls via the Suzuki Coupling Reaction of Aryl Triflates in a Biphasic Solvent System

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Abstract: A one-pot synthetic procedure for 2,2′-disubstituted biaryls was developed via a Suzuki cross-coupling reaction of aryl triflates in a biphasic solvent system. The effects of various bases and solvents were investigated. Results showed that the Na_2CO_3–toluene/H_2O combination gave the highest yields.

Keywords: Biphasic solvent, 2,2′-disubstituted biaryls, one-pot reaction, Suzuki coupling reaction, tetra(alkoxo)diboron

In our recent studies of serine protease inhibitors, we found an interesting biaryl compound **1**, which is prepared from the 2,2′,4,4′-tetrasubstituted analogue **2** (Scheme 1).[1] The functionalized 2,2′-disubstituted biaryls constitute an important class of compounds that includes numerous pharmacologically active products and various compounds with applications in materials.[2] Although the Suzuki cross-coupling reaction is one of the most efficient methods for the preparation of asymmetrical biaryls,[3] the synthesis of 2,2′-disubstituted biaryls is limited. Most of the methods require special ligands such as biphenyl-2-yl(dicyclohexyl)phosphine and

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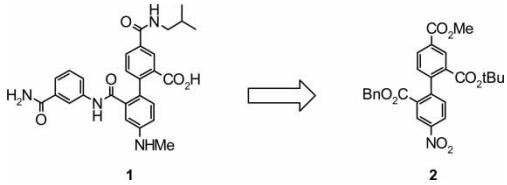
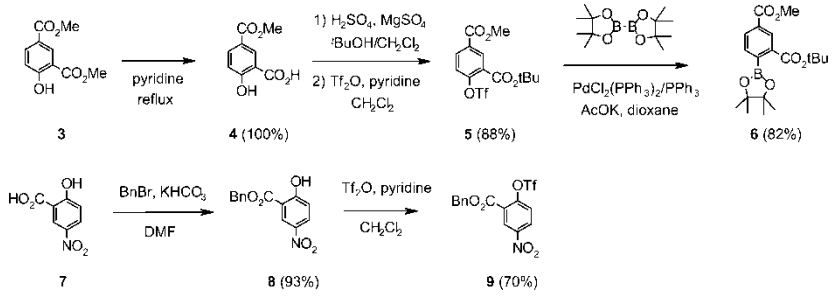


Scheme 1.

dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine for the coupling reaction[4] or have limited functional groups.[5]

Among several synthetic procedures for aryl boronic acids or esters,[6] the most useful method is based on the cross-coupling reaction of an aryl halide or aryl triflate with tetra(alkoxo)diboron in the presence of a palladium catalyst.[7] This method allows the use of commercially available bis(pinacolato)diboron, which is not only thermally stable but also insensitive to air and moisture. Moreover, this method can be utilized for the one-pot preparation of asymmetrical biaryls without the isolation of the aryl boronic esters.[8] On this basis, we planned to develop a method for the preparation of functionalized 2,2′-disubstituted biaryls by the use of bis(pinacolato)diboron.

We first tried to prepare the biaryl **2** based on a stepwise cross-coupling reaction. We employed an aryl triflate as the coupling reagent, because from the synthetic point of view, the use of aryl triflate had several advantages, including the easy access from phenols. The synthesis of the starting materials (**6** and **9**) is shown in Scheme 2. Dimethyl 4-hydroxyisophthalate **3** can be converted to the monomethyl ester **4** in pyridine under reflux conditions.[9] The monoacid **4** is protected by the *tert*-butyl group and converted to the corresponding triflate **5** by treatment with trifluoromethanesulfonic anhydride. At the borylation step, we employed a method reported by Ishiyama and coworkers, except for the particular palladium catalyst,[8a] and obtained the aryl boronate **6** in 82% yield. (In our preliminary work, the yield of the aryl boronate **6** was barely affected by use of palladium catalysts such as



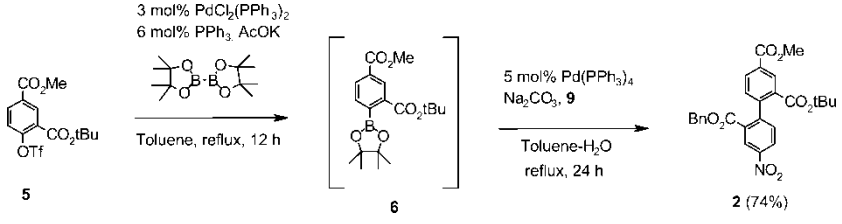
Scheme 2.

$PdCl_2(PPh_3)_2$ and $PdCl_2$(dppf), and so we selected $PdCl_2(PPh_3)_2$ with regard to cost.) The triflate **9** was synthesized in two steps from 2-hydroxy-5-nitrobenzoic acid **7**.

Next, the coupling reaction of the aryl boronate **6** with the triflate **9** was examined. In this step, the yield of biaryl **2** was affected by the base and solvent. When K_3PO_4 was employed as the base, biaryl **2** was obtained in only 45% yield, whereas the yield increased remarkably to more than 80% with weak bases such as K_2CO_3 and Na_2CO_3 in dioxane. Toluene was found to be more suitable as a solvent than dioxane and N,N-dimethylformamide (DMF). Thus, biaryl **2** was obtained in 87% yield in a reaction with Na_2CO_3 as base and toluene as solvent. This result suggests that mild reaction conditions might be suitable for the cross-coupling reaction, because of the base sensitivity of triflates.

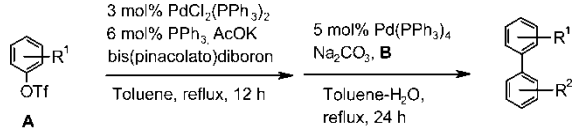
Encouraged by this result, we subsequently investigated the one-pot procedure from the triflate **5** to biaryl **2** (Scheme 3). To date, only two methods of one-pot biaryl synthesis using bis(pinacolato)diboron have been reported.[8] Ishiyama and coworkers reported an efficient in situ cross-coupling reaction of aryl triflates in the presence of K_3PO_4 for the second coupling reaction.[8a] Giroux and coworkers described a one-pot preparation of biaryls using DMF/H_2O as a solvent.[8b] As described in Table 1, obtaining biaryl **2** in high yield requires the use of a toluene–weak base system. However, because these prior methods used K_3PO_4 as a base or DMF as a solvent, we could not utilize them for the one-pot synthesis of biaryl **2**. We therefore attempted to apply our toluene–weak base system to one-pot biaryl synthesis. That is, after coupling between the triflate **5** and bis(pinacolato)diboron in toluene, another triflate **9** was added in the presence of Na_2CO_3 without isolation of the aryl boronate **6**. It is noteworthy that the desired biaryl **2** is not obtained in the toluene alone, but that the addition of H_2O in the second cross-coupling reaction affords biaryl **2** in 74% yield without hydrolysis of the ester groups. The reason why addition of H_2O produces a good result is not clearly understood. The yield substantially decreased without addition of another palladium catalyst for the second cross-coupling reaction.

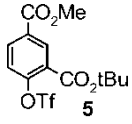
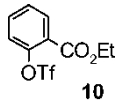
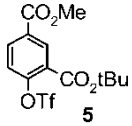
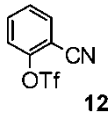
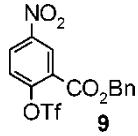
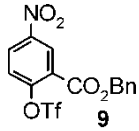
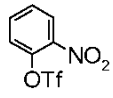
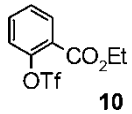
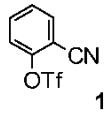
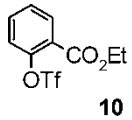
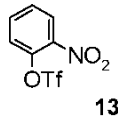
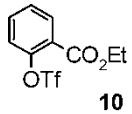
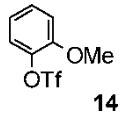
Various asymmetrical biaryls were synthesized by this one-pot procedure in a biphasic solvent system (Table 1). Cross-coupling between variously substituted aryl triflates proceeded in good yield (runs 1–7), whereas with the



Scheme 3.

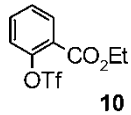
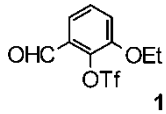
Table 1. Cross-coupling reactions of various aryl triflates using the one-pot procedure



Run	A	B	Yield (%)
1	 **5**	 **10**	69
2	 **5**	 **11**	79
3	 **12**	 **9**	72
4	 **11**	 **9**	79
5	 **12**	 **13**	88 (37)[8a] (0)[8b]
6	 **10**	 **12**	84
7	 **10**	 **13**	80
8	 **10**	 **14**	45

(*continued*)

Table 1. Continued

Run	A	B	Yield (%)
9	 **10**	 **15**	86

Notes. Yield of isolated products is based on the triflates used for the second coupling reaction. Yields obtained using reported methods are shown in parentheses. 8a) K_3PO_4-dioxane combination for the second cross-coupling reaction. 8b) Na_2CO_3–DMF/H_2O combination for the second cross-coupling reaction; 2.0 eq. of triflate **13** was employed.

prior methods (K_3PO_4–dioxane combination[8a] and Na_2CO_3–DMF/H_2O combination[8b] for the second cross-coupling reaction) the yield decreased to 37% and 0%, respectively (run 5). As is often the case with cross-coupling reaction of the electron-rich substituent,[3] the triflate **14** reacted more slowly to result in a reduced yield for the corresponding product (run 8). Interestingly, the ortho-disubstituted triflate **15** reacted and ortho-trisubstituted biaryl was obtained without difficultly (run 9).

In conclusion, we have modified the one-pot Suzuki cross-coupling reaction by the use of a biphasic solvent system. This method allows the preparation of asymmetrical biaryls from aryl triflates with various functional groups, including CO_2Et, CN, NO_2, and CHO, and even from those with substituents in the ortho position.

GENERAL PROCEDURE

Melting points were determined on a Yanaco micromelting apparatus or Büchi melting-point apparatus B-545 and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were obtained in $CDCl_3$ or dimethylsulfoxide-d_6 (DMSO-d_6) using a Jeol JNM-EX400, JNM-GX500, or JNM-A500 spectrometer. Chemical shifts were recorded in parts per million (δ), downfield relative to tetramethylsilane as the internal standard. Mass spectra (MS) were recorded on a Jeol JMS-DX300 or a Hitachi M-80 mass spectrometer. Elemental analysis was carried out on Yanaco MT-3 or MT-5 CHN analyzer and a Yokogawa IC7000S ion chromatoanalyzer. Chromatographic separations were performed using a silica-gel column (Merck Kieselgel 60).

2-Hydroxy-5-(methoxycarbonyl)benzoic Acid (4)

Pyridine (500 mL) was added to **3** (36.0 g, 171 mmol), and the mixture was refluxed for 17 h. The mixture was then concentrated in vacuo, and the

residue was acidified with 1 M HCl/H_2O (200 mL). The resulting precipitate was filtered, washed with H_2O, and dried in vacuo to give **4** (33.4 g, 100%) as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.84 (3H, s), 7.07 (1H, d, $J = 8.8$ Hz), 8.06 (1H, dd, $J = 2.2$ Hz, 8.8 Hz), 8.39 (1H, d, $J = 2.2$ Hz); FAB-MS (m/z): 197 $(M + H)^+$.

3-*tert*-Butyl 1-Methyl 4-{[(Trifluoromethyl)sulfonyl]oxy}-isophthalate (5)

Conc. H_2SO_4 (5.9 mL, 111 mmol) and 2-methylpropan-2-ol (53.0 mL, 554 mmol) were added to a solution of **4** (10.0 g, 51.0 mmol) and $MgSO_4$ (53.4 g, 444 mmol) in CH_2Cl_2 (500 mL), and the mixture was stirred at room temperature for 12 h. The mixture was then filtered and partitioned between $CHCl_3$ and 5% $NaHCO_3$ in H_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a colorless oil (9.91 g). Trifluoromethanesulfonic anhydride (13.0 mL, 77.3 mmol) was added to a solution of the compound obtained above (9.90 g) and pyridine (16.0 mL, 197 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred at room temperature for 30 min. The mixture was partitioned between CH_2Cl_2 and H_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt = 9 : 1) to give **5** (13.3 g, 88%) as a colorless oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.58 (9H, s), 3.91 (3H, s), 7.72 (1H, d, $J = 8.6$ Hz), 8.30 (1H, dd, $J = 2.4$ Hz, 8.6 Hz), 8.43 (1H, d, $J = 2.4$ Hz); FAB-MS (m/z): 385 $(M + H)^+$.

3-*tert*-Butyl 1-Methyl 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)isophthalate (6)

AcOK (3.09 g, 31.5 mmol) was added to a stirred solution of **5** (8.07 g, 21.0 mmol), bis(pinacolato)diboron (5.85 g, 23.1 mmol), PPh_3 (330 mg, 1.26 mmol), and $PdCl_2(PPh_3)_2$ (442 mg, 0.630 mmol) in 1,4-dioxane (130 ml) at room temperature under an argon atmosphere. The mixture was stirred at 80°C for 12 h and then concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt = 9 : 1) to give **6** (6.26 g, 82%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.33 (12H, s), 1.57 (9H, s), 3.89 (3H, s), 7.61 (1H, d, $J = 7.7$ Hz), 8.12 (1H, dd, $J = 1.5$ Hz, 7.7 Hz), 8.28 (1H, d, $J = 1.5$ Hz); FAB-MS (m/z): 363 $(M + H)^+$.

Benzyl 2-Hydroxy-5-nitrobenzoate (8)

To a solution of **7** (49.8 g, 271 mmol) and $KHCO_3$ (32.5 g, 325 mmol) in DMF (270 mL) was added benzyl bromide (38.6 mL, 325 mmol), and the

mixture was stirred at room temperature for 12 h. The mixture was partitioned between AcOEt and 5% $NaHCO_3$ in H_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give **8** (68.6 g, 93%) as a yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.40 (2H, s), 7.19 (1H, d, $J = 9.2$ Hz), 7.33–7.47 (3H, m), 7.47–7.55 (2H, m), 8.33 (1H, dd, $J = 2.9$ Hz, 9.2 Hz), 8.54 (1H, d, $J = 2.9$ Hz), 11.61 (1H, br s); FAB-MS (m/z): 272 $(M\text{-}H)^-$.

Benzyl 5-Nitro-2-{[(trifluoromethyl)sulfonyl]oxy}benzoate (9)

Trifluoromethanesulfonic anhydride (13.8 mL, 82.0 mmol) was added to a solution of **8** (14.9 g, 54.5 mmol) and pyridine (8.8 mL, 109 mmol) in CH_2Cl_2 (300 mL), and the mixture was stirred at room temperature for 30 min. The mixture was partitioned between CH_2Cl_2 and H_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt = 9 : 1) to give **9** (11.2 g, 51%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.44 (2H, s), 7.35–7.53 (5H, m), 7.92 (1H, d, $J = 9.2$ Hz), 8.63 (1H, dd, $J = 2.8$ Hz, 9.2 Hz), 8.73 (1H, d, $J = 2.8$ Hz).

Ethyl 2-{[(Trifluoromethyl)sulfonyl]oxy}benzoate (10)

Compound **10** was synthesized from ethyl salicylate according to the same procedure as that for **9**. Compound **10** was obtained as a colorless oil (99% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.33 (3H, t, $J = 7.1$ Hz), 4.36 (2H, q, $J = 7.1$ Hz), 7.57 (1H, d, $J = 8.2$ Hz), 7.62–7.70 (1H, m), 7.80–7.88 (1H, m), 8.07 (1H, d, $J = 7.9$ Hz); FAB-MS (m/z): 299 $(M + H)^+$.

2-Methylphenyl Trifluoromethanesulfonate (11)

Compound **11** was synthesized from *o*-cresol according to the same procedure as that for **9**. Compound **11** was obtained as a colorless oil (73% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.34 (3H, s), 7.34–7.44 (3H, m), 7.46–7.51 (1H, m); GC-MS (m/z): 240 $(M)^+$.

2-Cyanophenyl Trifluoromethanesulfonate (12)

Compound **12** was synthesized from 2-hydroxybenzonitrile according to the same procedure as that for **9**. Compound **12** was obtained as a colorless oil

(95% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.69–7.77 (1H, m), 7.83 (1H, d, $J = 8.4$ Hz), 7.92–8.00 (1H, m), 8.16 (1H, d, $J = 7.7$ Hz); ESI-MS (m/z): 252 $(M + H)^+$.

2-Nitrophenyl Trifluoromethanesulfonate (13)

Compound **13** was synthesized from 2-nitrophenol according to the same procedure as that for **9**. Compound **13** was obtained as a colorless oil (100% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.76–7.85 (2H, m), 7.95–8.03 (1H, m), 8.35 (1H, d, $J = 8.3$ Hz); FAB-MS (m/z): 272 $(M + H)^+$.

2-Methoxyphenyl Trifluoromethanesulfonate (14)

Compound **14** was synthesized from 2-methoxyphenol according to the same procedure as that for **9**. Compound **14** was obtained as a colorless oil (96% yield): ^{1}HNMR (300 MHz, DMSO-d_6) δ: 3.90 (3H, s), 7.04–7.10 (1H, m), 7.33 (1H, d, $J = 8.3$ Hz), 7.40–7.48 (2H, m); EI-MS (m/z): 256 $(M)^+$.

2-Ethoxy-6-Formylphenyl Trifluoromethanesulfonate (15)

Compound **15** was synthesized from 3-ethoxy-2-hydroxybenzaldehyde according to the same procedure as that for **9**. Compound **15** was obtained as a colorless solid (69% yield): ^{1}HNMR (300 MHz, DMSO-d_6) δ: 1.38 (3H, t, $J = 7.0$ Hz), 4.23 (2H, q, $J = 7.0$ Hz), 7.57–7.62 (1H, m), 7.65–7.70 (2H, m), 10.07 (1H, s).

GENERAL PROCEDURE FOR THE ONE-POT SUZUKI COUPLING REACTION OF ARYL TRIFLATES IN A BIPHASIC SOLVENT SYSTEM

AcOK (1.5 mmol) was added to a stirred solution of the triflate **A** (1.1 mmol), bis(pinacolato)diboron (1.2 mmol), PPh_3 (0.06 mmol), and $PdCl_2(PPh_3)_2$ (0.03 mmol) in toluene (10 ml) at room temperature under an argon atmosphere. The mixture was refluxed overnight, and then the triflate **B** (1.0 mmol), $Pd(PPh_3)_4$ (0.05 mmol), and 2 mol dm^{-3} aq. Na_2CO_3 (4 ml) were added to the reaction mixture. The solution was refluxed overnight. The mixture was extracted with AcOEt, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt) to give the target biaryl.

2′-Benzyl 2-*tert*-Butyl 4-Methyl 4′-Nitrobiphenyl-2,2′, 4-tricarboxylate (2)

Colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.15 (9H, s), 3.93 (3H, s), 5.05 (2H, s), 7.04–7.11 (2H, m), 7.20–7.30 (3H, m), 7.33 (1H, d, $J = 8.1$ Hz), 7.56 (1H, d, $J = 8.4$ Hz), 8.05 (1H, dd, $J = 1.5$ Hz, 8.1 Hz), 8.28 (1H, d, $J = 1.5$ Hz), 8.44 (1H, dd, $J = 2.3$ Hz, 8.4 Hz), 8.72 (1H, d, $J = 2.3$ Hz); FAB-MS (m/z): 491 $(M)^-$; HRMS (FAB) calcd. for $C_{27}H_{25}NO_8$: 491.1580; found: 491.1588.

2-*tert*-Butyl 2′-Ethyl 4-Methyl Biphenyl-2,2′,4-tricarboxylate (Run 1)

Colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.90 (3H, t, $J = 7.1$ Hz), 1.11 (9H, s), 3.91 (3H, s), 3.95 (2H, q, $J = 7.1$ Hz), 7.25 (1H, d, $J = 7.5$ Hz), 7.36 (1H, d, $J = 7.9$ Hz), 7.52–7.60 (1H, m), 7.62–7.70 (1H, m), 7.97 (1H, d, $J = 7.9$ Hz), 8.11 (1H, dd, $J = 1.8$ Hz, 7.9 Hz), 8.35 (1H, d, $J = 1.8$ Hz); FAB-MS (m/z): 385 $(M + H)^+$; anal. calcd. for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29; found: C, 68.60; H, 6.23.

2-*tert*-Butyl 4-Methyl 2′-Methylbiphenyl-2,4-dicarboxylate (Run 2)

Colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.12 (9H, s), 2.02 (3H, s), 3.91 (3H, s), 7.04 (1H, d, $J = 7.3$ Hz), 7.20–7.36 (3H, m), 7.41 (1H, d, $J = 8.0$ Hz), 8.13 (1H, dd, $J = 1.8$ Hz, 8.0 Hz), 8.29 (1H, d, $J = 1.8$ Hz); FAB-MS (m/z): 327 $(M + H)^+$; anal. calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.78; found: C, 73.30; H, 6.78.

Benzyl 2′-Cyano-4-nitrobiphenyl-2-carboxylate (Run 3)

Yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.16 (2H, s), 7.16–7.25 (2H, m), 7.30–7.37 (3H, m), 7.48 (1H, d, $J = 7.9$ Hz), 7.54–7.62 (1H, m), 7.70–7.79 (2H, m), 7.87 (1H, d, $J = 7.7$ Hz), 8.54 (1H, dd, $J = 2.2$ Hz, 8.4 Hz), 8.73 (1H, d, $J = 2.2$ Hz); ESI-MS (m/z): 359 $(M + H)^+$; HRMS (FAB) calcd. for $C_{21}H_{14}N_2O_4$: 358.0954; found: 358.0963.

Benzyl 2′-Methyl-4-nitrobiphenyl-2-carboxylate (Run 4)

Yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.97 (3H, s), 5.07 (1H, d, $J = 13.7$ Hz), 5.12 (1H, d, $J = 13.7$ Hz), 7.03–7.13 (3H, m), 7.19–7.26 (2H, m), 7.27–7.35 (4H, m), 7.59 (1H, d, $J = 8.4$ Hz), 8.44 (1H, dd, $J = 2.6$ Hz, 8.4 Hz), 8.63 (1H, d, $J = 2.6$ Hz); FAB-MS (m/z): 348

$(M + H)^+$; anal. calcd. for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.01; found: C, 72.50; H, 4.94; N, 4.01.

2′-Nitrobiphenyl-2-carbonitrile (Run 5)

Pale yellow crystals: mp 128–130°C (AcOEt–hexane) (lit.[10] mp 128–131°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.55 (1H, d, $J = 7.7$ Hz), 7.59–7.69 (2H, m), 7.76–7.84 (2H, m), 7.86–7.94 (1H, m), 7.79 (1H, d, $J = 7.7$ Hz), 8.24 (1H, d, $J = 8.1$ Hz); ESI-MS (m/z): 225 $(M + H)^+$; anal. calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.60; N, 12.49; found: C, 69.55; H, 3.73; N, 12.48.

Ethyl 2′-Nitrobiphenyl-2-carboxylate (Run 6)

Yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.94 (3H, t, $J = 7.1$ Hz), 3.98 (2H, q, $J = 7.1$ Hz), 7.33 (1H, d, $J = 7.7$ Hz), 7.37 (1H, d, $J = 7.5$ Hz), 7.53–7.61 (1H, m), 7.62–7.73 (2H, m), 7.73–7.81 (1H, m), 7.98 (1H, d, $J = 7.7$ Hz), 8.12 (1H, d, $J = 8.1$ Hz); FAB-MS (m/z): 272 $(M + H)^+$; anal. calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57; found: C, 76.37; H, 5.19; N, 5.55.

Ethyl 2′-Cyanobiphenyl-2-carboxylate (Run 7)

Colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.96 (3H, t, $J = 7.4$ Hz), 4.04 (2H, q, $J = 7.4$ Hz), 7.42 (1H, d, $J = 7.7$ Hz), 7.43 (1H, d, $J = 7.7$ Hz), 7.54–7.67 (2H, m), 7.69–7.79 (2H, m), 7.90 (1H, d, $J = 7.7$ Hz), 8.01 (1H, d, $J = 7.7$ Hz); FAB-MS (m/z): 252 $(M + H)^+$; anal. calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16; found: C, 66.37; H, 4.84; N, 5.15.

Ethyl 2′-Methoxybiphenyl-2-carboxylate (Run 8)

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.02 (3H, t, $J = 7.1$ Hz), 3.71 (3H, s), 4.08 (2H, q, $J = 7.1$ Hz), 6.89 (1H, d, $J = 8.1$ Hz), 6.99–7.06 (1H, m), 7.21–7.27 (2H, m), 7.29–7.44 (2H, m), 7.48–7.57 (1H,m), 7.87 (1H, d, $J = 7.8$ Hz); FAB-MS (m/z): 257 $(M + H)^+$; HRMS (FAB) calcd. for $C_{16}H_{16}O_3$: 257.1178; found: 257.1176.

Ethyl 2′-Ethoxy-6′-formylbiphenyl-2-carboxylate (Run 9)

Colorless crystals; mp 75–76°C (hexane); ^{1}HNMR (300 MHz, DMSO-d_6) δ: 0.89 (3H, d, $J = 7.1$ Hz), 1.08 (3H, d, $J = 6.9$ Hz), 3.88–4.06 (4H,

m), 7.26 (1H, d, $J = 7.5$ Hz), 7.31–7.36 (1H, m), 7.47–7.59 (3H, m), 7.61–7.68 (1H, m), 7.94 (1H, d, $J = 7.5$ Hz), 9.62 (1H, s); FAB-MS (m/z): 299 $(M + H)^+$; HRMS (FAB) calcd. for $C_{18}H_{18}O_4$: 299.1283; found: 299.1294.

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